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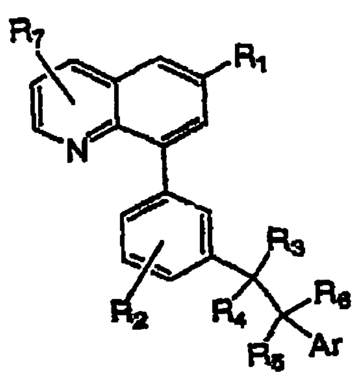
(54) Title: SUBSTITUTED 8-ARYLQUINOLINE PDE4 INHIBITORS



(I)

(57) Abstract: 8-arylquinolines of formula(I) wherein the aryl group at the 8-position contains a *meta* two atom bridge to an optionally substituted phenyl or pyridyl group, are PDE4 inhibitors useful to treat asthma, chronic bronchitis, chronic obstructive pulmonary disease, arthritis, respiratory distress syndrome, allergic rhinitis, neurogenic inflammation, pain, rheumatoid arthritis, and other diseases. R^1-R^7 and Ar are as in claim 1.

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TITLE OF THE INVENTION

SUBSTITUTED 8-ARYLQUINOLINE PDE4 INHIBITORS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention is directed to compounds that are substituted 8-arylquinolines. In particular, this invention is directed to substituted 8-arylquinolines which are phosphodiesterase-4 inhibitors wherein the aryl group at the 8-position contains a *meta* two carbon atom bridge to an optionally substituted phenyl or pyridyl group.

RELATED BACKGROUND

Hormones are compounds that variously affect cellular activity. In many respects, hormones act as messengers to trigger specific cellular responses and activities. Many effects produced by hormones, however, are not caused by the singular effect of just the hormone. Instead, the hormone first binds to a receptor, thereby triggering the release of a second compound that goes on to affect the cellular activity. In this scenario, the hormone is known as the first messenger while the second compound is called the second messenger. Cyclic adenosine monophosphate (adenosine 3', 5'-cyclic monophosphate, "cAMP" or "cyclic AMP") is known as a second messenger for hormones including epinephrine, glucagon, calcitonin, corticotrophin, lipotropin, luteinizing hormone, norepinephrine, parathyroid hormone, thyroid-stimulating hormone, and vasopressin. Thus, cAMP mediates cellular responses to hormones. Cyclic AMP also mediates cellular responses to various neurotransmitters.

Phosphodiesterases ("PDE") are a family of enzymes that metabolize 3', 5' cyclic nucleotides to 5' nucleoside monophosphates, thereby terminating cAMP second messenger activity. A particular phosphodiesterase, phosphodiesterase-4 ("PDE4", also known as "PDE-IV"), which is a high affinity, cAMP specific, type IV PDE, has generated interest as potential targets for the development of novel anti-asthmatic and anti-inflammatory compounds. PDE4 is known to exist as at lease four isoenzymes, each of which is encoded by a distinct gene. Each of the four known PDE4 gene products is believed to play varying roles in allergic and/or inflammatory

responses. Thus, it is believed that inhibition of PDE4, particularly the specific PDE4 isoforms that produce detrimental responses, can beneficially affect allergy and inflammation symptoms. It would be desirable to provide novel compounds and compositions that inhibit PDE4 activity.

Inhibition of PDE4 activity is believed effective for the treatment of osteoporosis by reducing bone loss. For example, Ken-ici Miyamoto et al., Biochem. Pharmacology, 54:613-617(1997) describes the effect of a PDE4 on bone loss. Therefore, it would be desirable to provide novel compounds and compositions that inhibit PDE4 activity.

A major concern with the use of PDE4 inhibitors is the side effect of emesis which has been observed for several candidate compounds as described in C.Burnouf et al. *Ann. Rep. In Med. Chem.*, 33:91-109(1998). B.Hughes et al., *Br. J.Pharmacol.*, 118:1183-1191(1996); M.J.Perry et al., *Cell Biochem. Biophys.*, 29:113-132(1998); S.B.Christensen et al., *J.Med. Chem.*, 41:821-835(1998); and Burnouf (*Ibid.*)describe the wide variation of the severity of the undesirable side effects exhibited by various compounds. As described in M.D.Houslay et al., *Adv. In Pharmacol.*, 44:225-342(1998) and D.Spina et al., *Adv. In Pharmacol.*, 44:33-89(1998), there is great interest and research of therapeutic PDE4 inhibitors.

International Patent Publication WO9422852 describes quinolines as PDE4 inhibitors.

A.H.Cook, et al., *J.Chem. Soc.*, 413-417(1943) describes gamma-pyridylquinolines. Other quinoline compounds are described in Kei Manabe et al., *J.Org. Chem.*, 58(24):6692-6700(1993); Kei Manabe et al., *J.Am. Chem. Soc.*, 115(12):5324-5325(1993); and Kei Manabe et al., *J.Am. Chem. Soc.*, 114(17):6940-6941(1992).

Compounds that include ringed systems are described by various investigators as effective for a variety of therapies and utilities. For example, International Patent Publication No. WO 98/25883 describes ketobenzamides as calpain inhibitors, European Patent Publication No. EP 811610 and U.S. Patent Nos. 5,679,712, 5,693,672 and 5,747,541describe substituted benzoylguanidine sodium channel blockers, U.S. Patent No. 5,736,297 describes ring systems useful as a photosensitive composition.

U.S. Patent Nos. 5,491,147, 5,608,070, 5,622,977, 5,739,144, 5,776,958, 5,780,477, 5,786,354, 5,798,373, 5,849,770, 5,859,034, 5,866,593, 5,891,896, and International Patent Publication WO 95/35283 describe PDE4

inhibitors that are tri-substituted aryl or heteroaryl phenyl derivatives. U.S. Patent No. 5,580,888 describes PDE4 inhibitors that are styryl derivatives. U.S. Patent No. 5,550,137 describes PDE4 inhibitors that are phenylaminocarbonyl derivatives. U.S. Patent No. 5,340,827 describes PDE4 inhibitors that are phenylcarboxamide compounds. U.S. Patent No. 5,780,478 describes PDE4 inhibitors that are tetra-substituted phenyl derivatives. International Patent Publication WO 96/00215 describes substituted oxime derivatives useful as PDE4 inhibitors. U.S. Patent No. 5,633,257 describes PDE4 inhibitors that are cyclo(alkyl and alkenyl)phenyl-alkenyl (aryl and heteroaryl) compounds.

However, there remains a need for novel compounds and compositions that therapeutically inhibit PDE4 with minimal side effects.

SUMMARY OF THE INVENTION

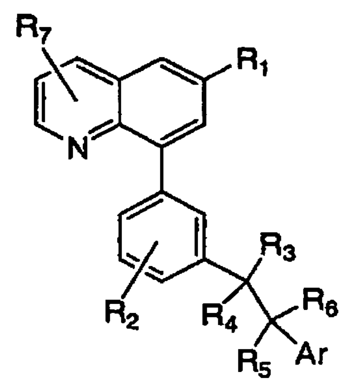
The present invention is directed to novel substituted 8-arylquinolines that are PDE4 inhibitors, wherein the aryl group at the 8-position contains a *meta* two carbon atom bridge to an optionally substituted phenyl or pyridyl group. This invention also provides a pharmaceutical composition which includes an effective amount of the novel substituted 8-arylquinoline and a pharmaceutically acceptable carrier.

This invention further provides a method of treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord

trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues by the administration of an effective amount of the novel substituted 8-arylquinoline or a precursor compound which forms *in vivo* the novel substituted 8-arylquinoline.

DETAILED DESCRIPTION OF THE INVENTION

A compound of this invention is represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, pyridinone, pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-5 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is hydrogen, halogen; or a –C_{1-6}alkyl, –cycloC_{3-6}alkyl, -C_{1-6}alkenyl, –C_{0-4}alkyl–C(O)–C_{0-4}alkyl, –C_{1-6}alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, –C_{1-6}alkylamino, –(C_{1-6}alkyl)(C_{1-6}alkyl)amino, -C_{1-6}alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), –SO_nNH(aryl), -SO_nNH(heteroaryl), –SO_nNH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, –(C_{1-6}alkyl)–O–C(CN)–dialkylamino, or –(C_{0-6}alkyl)–SO_n–(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, –C_1-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl,

alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or –SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or OH;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF_3,–SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH

R_5 is hydrogen, hydroxyl, –CN; or a –C_{1-6}alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, –C_{1-6}alkyl–C_{3-7}cycloalkyl, –C_{1-6}alkyl(C_{3-7}cycloalkyl)$_2$, –C_{1-6}alkyl-aryl, –C(O)–N(C_{0-6}alkyl)$_2$, –SO_naryl, –SO_n–C_{1-6}alkyl, –SO_n–C_{3-7}cycloalkyl, –SO_n–N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, –P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O)–O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –CH_2– or –O–; and

n is 0, 1, or 2.

In one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, optionally substituted with 1-3 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is hydrogen, halogen; or a –C_{1-6}alkyl, –cycloC_{3-6}alkyl, -C_{1-6}alkenyl, –C_{0-4}alkyl–C(O)–C_{0-4}alkyl, –C_{1-6}alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, –C_{1-6}alkylamino, –(C_{1-6}alkyl)(C_{1-6}alkyl)amino,

-C_{1-6}alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), –SO_nNH(aryl), -SO_nNH(heteroaryl), –SO_nNH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, –(C_{1-6}alkyl)–O–C(CN)–dialkylamino, or –(C_{0-6}alkyl)–SO_n–(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, –C_1-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or –SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF_3,–SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R5 is hydrogen, hydroxyl, –CN; or a –C_{1-6}alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, –C_{1-6}alkyl–C_{3-7}cycloalkyl, –C_{1-6}alkyl(C_{3-7}cycloalkyl)$_2$, –C_{1-6}alkyl-aryl, –C(O)–N(C_{0-6}alkyl)$_2$, –SO_naryl, –SO_n–C_{1-6}alkyl, –SO_n–C_{3-7}cycloalkyl, –SO_n–N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, –P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O)–O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –CH_2– or –O–; and

n is 0, 1, or 2.

In an embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, optionally substituted with 1-3 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with

C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is hydrogen, halogen; or a $-C_{1-6}$alkyl, $-$cycloC_{3-6}alkyl, $-C_{1-6}$alkenyl, $-C_{0-4}$alkyl$-$C(O)$-C_{0-4}$alkyl, $-C_{1-6}$alkoxy, aryl, heteroaryl, $-$CN, -heterocycloC_{3-6}alkyl, $-$amino, $-C_{1-6}$alkylamino, $-(C_{1-6}$alkyl)(C_{1-6}alkyl)amino, $-C_{1-6}$alkyl(oxy)C_{1-6}alkyl, $-$C(O)NH(aryl), $-$C(O)NH(heteroaryl), $-SO_n$NH(aryl), $-SO_n$NH(heteroaryl), $-SO_n$NH(C_{1-6}alkyl), $-$C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-$SO_n$$-$($C_{1-6}$alkyl), $-$carbamoyl, $-$(C_{1-6}alkyl)$-$O$-$C(CN)$-$dialkylamino, or $-$(C_{0-6}alkyl)$-SO_n-$(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, $-$OH, -CN, $-C_1$-C_6alkyl, $-$C(O)(heterocycloC_{3-6}alkyl), $-$C(O)$-$O$-$(C_{0-6}alkyl), $-$C(O)$-$O$-$aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, $-$cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n-$(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, $-$CN, or $-$C(O)$-$O$-C_{0-6}$alkyl, wherein the -C(O)$-$O$-C_{0-6}$alkyl is optionally substituted with 1-3 independent halogen, CN, CF_3,$-SO_n-C_{1-6}$alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R_5 is hydrogen, hydroxyl, $-$CN; or a $-C_{1-6}$alkyl, $-$C(O)C_{1-6}alkyl, -C(O)-aryl, $-$C(O)$-$pyridyl, $-$C(O)$-$O$-C_{0-6}$alkyl, $-$C(O)$-C_{3-7}$cycloalkyl, $-C_{1-6}$alkyl$-C_{3-7}$cycloalkyl, $-C_{1-6}$alkyl(C_{3-7}cycloalkyl)$_2$, $-C_{1-6}$alkyl-aryl, $-$C(O)$-$N(C_{0-6}alkyl)$_2$, $-SO_n$aryl, $-SO_n-C_{1-6}$alkyl, $-SO_n-C_{3-7}$cycloalkyl, $-SO_n-$N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, $-$P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, $-SO_n$imidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or Nor oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, $-$CN, -CF_3, $-C_{1-6}$alkyl, $-SO_n-C_{1-6}$alkyl, $-$C(O) $-$O$-C_{0-6}$alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form $-CH_2-$ or $-$O$-$; and

n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, optionally substituted with 1-3 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is hydrogen, halogen; or a –C_{1-6}alkyl, –cycloC_{3-6}alkyl, -C_{1-6}alkenyl, –C_{0-4}alkyl–C(O)–C_{0-4}alkyl, –C_{1-6}alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, –C_{1-6}alkylamino, –(C_{1-6}alkyl)(C_{1-6}alkyl)amino, -C_{1-6}alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), –SO_nNH(aryl), -SO_nNH(heteroaryl), –SO_nNH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, –(C_{1-6}alkyl)–O–C(CN)–dialkylamino, or –(C_{0-6}alkyl)–SO_n–(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, –C_1-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or –SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is oxadiazolyl optionally substituted with 1-3 independent halogen, CN, CF_3,–SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R_5 is hydrogen, hydroxyl, –CN; or a –C_{1-6}alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, –C_{1-6}alkyl–C_{3-7}cycloalkyl, –C_{1-6}alkyl(C_{3-7}cycloalkyl)$_2$, –C_{1-6}alkyl-aryl, –C(O)–N(C_{0-6}alkyl)$_2$, –SO_naryl, –SO_n–C_{1-6}alkyl, –SO_n–C_{3-7}cycloalkyl, –SO_n–N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, –P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O) –O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form $-CH_2-$ or –O–; and

n is 0, 1, or 2.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, optionally substituted with 1-3 independent $-C_{1-6}$alkyl, -OH, -CN, halogen, $-CF_3$, $-(C_{0-6}$alkyl)-SO_n-(C_{1-6}alkyl), $-(C_{0-6}$alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is hydrogen, halogen; or a $-C_{1-6}$alkyl, –cycloC_{3-6}alkyl, $-C_{1-6}$alkenyl, $-C_{0-4}$alkyl–C(O)–C_{0-4}alkyl, $-C_{1-6}$alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, $-C_{1-6}$alkylamino, $-(C_{1-6}$alkyl)(C_{1-6}alkyl)amino, $-C_{1-6}$alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), $-SO_n$NH(aryl), $-SO_n$NH(heteroaryl), $-SO_n$NH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, $-(C_{1-6}$alkyl)–O–C(CN)–dialkylamino, or $-(C_{0-6}$alkyl)–SO_n–(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, $-C_1$-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n$–(C_{1-6}alkyl);

R_2 and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF3,$-SO_n$–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R5 is hydrogen, hydroxyl, –CN; or a $-C_{1-6}$alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl–

C_{3-7}cycloalkyl, $-C_{1-6}$alkyl(C_{3-7}cycloalkyl)$_2$, $-C_{1-6}$alkyl-aryl, $-C(O)-N(C_{0-6}$alkyl)$_2$, $-SO_n$aryl, $-SO_n-C_{1-6}$alkyl, $-SO_n-C_{3-7}$cycloalkyl, $-SO_n-N(C_{0-6}$alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, -P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, $-SO_n$imidazolyl, $-SO_n$thiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, $-CF_3$, $-C_{1-6}$alkyl, $-SO_n-C_{1-6}$alkyl, –C(O) $-O-C_{0-6}$alkyl, or hydroxyC_{1-6}alkyl substituents;

R_6 and R_3 form $-CH_2-$; and

n is 0, 1, or 2.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein Ar is phenyl, optionally substituted with 1-3 independent $-C_{1-6}$alkyl, -OH, -CN, halogen, $-CF_3$, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is $-C_{1-6}$alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, $-C_1-C_6$alkyl, -C(O)(heterocycloC_{3-6}alkyl), $-C(O)-O-(C_{0-6}$alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n-(C_{1-6}$alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or $-C(O)-O-C_{0-6}$alkyl, wherein the phenyl, oxadiazolyl, or $-C(O)-O-C_{0-6}$alkyl is optionally substituted with 1-3 independent halogen, CN, CF3,$-SO_n-C_{1-6}$alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH

R5 is hydrogen, hydroxyl, –CN; or a $-C_{1-6}$alkyl, $-C(O)C_{1-6}$alkyl, -C(O)-aryl, –C(O)–pyridyl, $-C(O)-O-C_{0-6}$alkyl, $-C(O)-C_{3-7}$cycloalkyl, $-C_{1-6}$alkyl–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl(C_{3-7}cycloalkyl)$_2$, $-C_{1-6}$alkyl-aryl, $-C(O)-N(C_{0-6}$alkyl)$_2$, $-SO_n$aryl, $-SO_n-C_{1-6}$alkyl, $-SO_n-C_{3-7}$cycloalkyl, $-SO_n-N(C_{0-6}$alkyl)$_2$,

-P(O)(C_1-6alkyl)2, –P(O)(C_1-6alkoxy)2, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF3, –C_1-6alkyl, –SO_n–C_1-6alkyl, –C(O) –O–C_0-6alkyl, or hydroxyC_1-6alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –CH_2– or –O–; and

n is 0, 1, or 2.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, optionally substituted with 1-3 independent -C_1-6alkyl, -OH, -CN, halogen, -CF_3, -(C_0-6alkyl)-SO_n-(C_1-6alkyl), -(C_0-6alkyl)-SO_n-NH-(C_1-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_1-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is –C_1-6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, –C_1-C_6alkyl, -C(O)(heterocycloC_3-6alkyl), –C(O)–O–(C_0-6alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_3-6alkyl, heterocycloC_3-6alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or –SO_n–(C_1-6alkyl);

R_2, and R_3 are each hydrogen;

R_4 is hydrogen;

R5 is hydrogen, hydroxyl, –CN; or a –C_1-6alkyl, –C(O)C_1-6alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_0-6alkyl, –C(O)–C_3-7cycloalkyl, –C_1-6alkyl–C_3-7cycloalkyl, –C_1-6alkyl(C_3-7cycloalkyl)2, –C_1-6alkyl-aryl, –C(O)–N(C_0-6alkyl)2, –SO_naryl, –SO_n–C_1-6alkyl, –SO_n–C_3-7cycloalkyl, –SO_n–N(C_0-6alkyl)2, -P(O)(C_1-6alkyl)2, –P(O)(C_1-6alkoxy)2, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_1-6alkyl, –SO_n–C_1-6alkyl, –C(O) –O–C_0-6alkyl, or hydroxyC_1-6alkyl substituents;

R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

or R_5 and R_6 form =O;

or R_6 and R_3 form $-CH_2-$ or $-O-$; and

n is 0, 1, or 2.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl substituted with $-(C_{0-6}$alkyl)-SO_n-$(C_{1-6}$alkyl), and the alkyl group is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is $-C_{1-6}$alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, $-C_1$-C_6alkyl, -C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n-(C_{1-6}$alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF_3,$-SO_n-C_{1-6}$alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH

R5 is hydrogen, hydroxyl, –CN; or a $-C_{1-6}$alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl(C_{3-7}cycloalkyl$)_2$, $-C_{1-6}$alkyl-aryl, –C(O)–N(C_{0-6}alkyl$)_2$, $-SO_n$aryl, $-SO_n-C_{1-6}$alkyl, $-SO_n-C_{3-7}$cycloalkyl, $-SO_n$–N(C_{0-6}alkyl$)_2$, -P(O)(C_{1-6}alkyl$)_2$, –P(O)(C_{1-6}alkoxy$)_2$, phenyl, pyridyl, $-SO_n$imidazolyl, $-SO_n$thiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, $-CF_3$, $-C_{1-6}$alkyl, $-SO_n-C_{1-6}$alkyl, –C(O) –O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form $-CH_2-$ or $-O-$; and

n is 0, 1, or 2.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl substituted with $-(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl)$, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is $-C_{1-6}alkyl$, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, $-C_1-C_6alkyl$, $-C(O)(heterocycloC_{3-6}alkyl)$, $-C(O)-O-(C_{0-6}alkyl)$, –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, $-cycloC_{3-6}alkyl$, $heterocycloC_{3-6}alkyl$, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n-(C_{1-6}alkyl)$;

R_2 and R_3 are each hydrogen;

R_4 is hydrogen;

R5 is hydrogen, hydroxyl, –CN; or a $-C_{1-6}alkyl$, $-C(O)C_{1-6}alkyl$, -C(O)-aryl, –C(O)–pyridyl, $-C(O)-O-C_{0-6}alkyl$, $-C(O)-C_{3-7}cycloalkyl$, $-C_{1-6}alkyl-C_{3-7}cycloalkyl$, $-C_{1-6}alkyl(C_{3-7}cycloalkyl)_2$, $-C_{1-6}alkyl$-aryl, $-C(O)-N(C_{0-6}alkyl)_2$, $-SO_naryl$, $-SO_n-C_{1-6}alkyl$, $-SO_n-C_{3-7}cycloalkyl$, $-SO_n-N(C_{0-6}alkyl)_2$, $-P(O)(C_{1-6}alkyl)_2$, $-P(O)(C_{1-6}alkoxy)_2$, phenyl, pyridyl, $-SO_nimidazolyl$, $-SO_nthiazolyl$, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, $-CF_3$, $-C_{1-6}alkyl$, $-SO_n-C_{1-6}alkyl$, $-C(O)-O-C_{0-6}alkyl$, or $hydroxyC_{1-6}alkyl$ substituents;

R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}alkyl$, or $-C_{1-6}alkoxy$, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

or R_5 and R_6 form =O;

or R_6 and R_3 form $-CH_2-$ or $-O-$; and

n is 0, 1, or 2.

In a second aspect of the invention, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is hydrogen, halogen; or a –C_{1-6}alkyl, –cycloC_{3-6}alkyl, -C_{1-6}alkenyl, –C_{0-4}alkyl–C(O)–C_{0-4}alkyl, –C_{1-6}alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, –C_{1-6}alkylamino, –(C_{1-6}alkyl)(C_{1-6}alkyl)amino, -C_{1-6}alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), –SO_nNH(aryl), -SO_nNH(heteroaryl), –SO_nNH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, –(C_{1-6}alkyl)–O–C(CN)–dialkylamino, or –(C_{0-6}alkyl)–SO_n–(C_{1-6}alkyl) group,. wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, –C_1-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or –SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF3,–SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R5 is hydrogen, hydroxyl, –CN; or a –C_{1-6}alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, –C_{1-6}alkyl–C_{3-7}cycloalkyl, –C_{1-6}alkyl(C_{3-7}cycloalkyl)$_2$, –C_{1-6}alkyl-aryl, –C(O)–N(C_{0-6}alkyl)$_2$, –SO_naryl, –SO_n–C_{1-6}alkyl, –SO_n–C_{3-7}cycloalkyl, –SO_n–N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, –P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O) –O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;
or R_6 and R_3 form $-CH_2-$ or –O–; and
n is 0, 1, or 2.

In an embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent $-C_{1-6}$alkyl, -OH, -CN, halogen, $-CF_3$, $-(C_{0-6}$alkyl)-SO_n-(C_{1-6}alkyl), $-(C_{0-6}$alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is hydrogen, halogen; or a $-C_{1-6}$alkyl, –cycloC_{3-6}alkyl, $-C_{1-6}$alkenyl, $-C_{0-4}$alkyl–C(O)–C_{0-4}alkyl, $-C_{1-6}$alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, $-C_{1-6}$alkylamino, $-(C_{1-6}$alkyl)(C_{1-6}alkyl)amino, $-C_{1-6}$alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), $-SO_n$NH(aryl), $-SO_n$NH(heteroaryl), $-SO_n$NH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, $-(C_{1-6}$alkyl)–O–C(CN)–dialkylamino, or $-(C_{0-6}$alkyl)–SO_n–(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, $-C_1$-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n$–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is phenyl optionally substituted with 1-3 independent halogen, CN, CF3,–SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R5 is hydrogen, hydroxyl, –CN; or a $-C_{1-6}$alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl(C_{3-7}cycloalkyl$)_2$, $-C_{1-6}$alkyl-aryl, –C(O)–N(C_{0-6}alkyl$)_2$, $-SO_n$aryl, $-SO_n$–C_{1-6}alkyl, $-SO_n$–C_{3-7}cycloalkyl, $-SO_n$–N(C_{0-6}alkyl$)_2$, -P(O)(C_{1-6}alkyl$)_2$, –P(O)(C_{1-6}alkoxy$)_2$, phenyl, pyridyl, $-SO_n$imidazolyl,

-SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O) –O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –CH_2– or –O–; and

n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is hydrogen, halogen; or a –C_{1-6}alkyl, –cycloC_{3-6}alkyl, -C_{1-6}alkenyl, –C_{0-4}alkyl–C(O)–C_{0-4}alkyl, –C_{1-6}alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, –C_{1-6}alkylamino, –(C_{1-6}alkyl)(C_{1-6}alkyl)amino, -C_{1-6}alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), –SO_nNH(aryl), -SO_nNH(heteroaryl), –SO_nNH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, –(C_{1-6}alkyl)–O–C(CN)–dialkylamino, or –(C_{0-6}alkyl)–SO_n–(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, –C_1-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or –SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3

independent halogen, CN, CF_3, $-SO_n-C_{1-6}$alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R5 is hydrogen, hydroxyl, –CN; or a $-C_{1-6}$alkyl, $-C(O)C_{1-6}$alkyl, -C(O)-aryl, –C(O)–pyridyl, $-C(O)-O-C_{0-6}$alkyl, $-C(O)-C_{3-7}$cycloalkyl, $-C_{1-6}$alkyl$-C_{3-7}$cycloalkyl, $-C_{1-6}$alkyl$(C_{3-7}$cycloalkyl$)_2$, $-C_{1-6}$alkyl-aryl, $-C(O)-N(C_{0-6}$alkyl$)_2$, $-SO_n$aryl, $-SO_n-C_{1-6}$alkyl, $-SO_n-C_{3-7}$cycloalkyl, $-SO_n-N(C_{0-6}$alkyl$)_2$, $-P(O)(C_{1-6}$alkyl$)_2$, $-P(O)(C_{1-6}$alkoxy$)_2$, phenyl, pyridyl, $-SO_n$imidazolyl, $-SO_n$thiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, $-CF_3$, $-C_{1-6}$alkyl, $-SO_n-C_{1-6}$alkyl, $-C(O)-O-C_{0-6}$alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form $-CH_2-$ or –O–; and

n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent $-C_{1-6}$alkyl, -OH, -CN, halogen, $-CF_3$, $-(C_{0-6}$alkyl$)-SO_n-(C_{1-6}$alkyl$)$, $-(C_{0-6}$alkyl$)-SO_n-NH-(C_{1-6}$alkyl$)$ or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is hydrogen, halogen; or a $-C_{1-6}$alkyl, $-$cycloC_{3-6}alkyl, $-C_{1-6}$alkenyl, $-C_{0-4}$alkyl$-C(O)-C_{0-4}$alkyl, $-C_{1-6}$alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, $-C_{1-6}$alkylamino, $-(C_{1-6}$alkyl$)(C_{1-6}$alkyl$)$amino, $-C_{1-6}$alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), $-SO_n$NH(aryl), $-SO_n$NH(heteroaryl), $-SO_n$NH$(C_{1-6}$alkyl$)$, $-C(O)N(C_{0-6}$alkyl$)(C_{0-6}$alkyl$)$, $-NH-SO_n-(C_{1-6}$alkyl$)$, –carbamoyl, $-(C_{1-6}$alkyl$)-O-C(CN)-$dialkylamino, or $-(C_{0-6}$alkyl$)-SO_n-(C_{1-6}$alkyl$)$ group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, $-C_1-C_6$alkyl, $-C(O)$(heterocycloC_{3-6}alkyl$)$, $-C(O)-O-(C_{0-6}$alkyl$)$, –C(O)–O–aryl,

alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n-(C_{1-6}$alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF_3,$-SO_n-C_{1-6}$alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R5 is hydrogen, hydroxyl, –CN; or a $-C_{1-6}$alkyl, $-C(O)C_{1-6}$alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl–C_{3-7}cycloalkyl, $-C_{1-6}$alkyl(C_{3-7}cycloalkyl$)_2$, $-C_{1-6}$alkyl-aryl, –C(O)–N(C_{0-6}alkyl$)_2$, $-SO_n$aryl, $-SO_n-C_{1-6}$alkyl, $-SO_n-C_{3-7}$cycloalkyl, $-SO_n-N(C_{0-6}$alkyl$)_2$, -P(O)(C_{1-6}alkyl$)_2$, –P(O)(C_{1-6}alkoxy$)_2$, phenyl, pyridyl, $-SO_n$imidazolyl, $-SO_n$thiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, $-CF_3$, $-C_{1-6}$alkyl, $-SO_n-C_{1-6}$alkyl, –C(O) –O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –O–; and

n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent $-C_{1-6}$alkyl, -OH, -CN, halogen, $-CF_3$, $-(C_{0-6}$alkyl$)-SO_n-(C_{1-6}$alkyl), $-(C_{0-6}$alkyl$)-SO_n-NH-(C_{1-6}$alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or $-CF_3$;

R_1 is $-C_{1-6}$alkyl or –cycloC_{3-6}alkyl, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, $-C_1-C_6$alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-}

6alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or -SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF_3,–SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH;

R5 is hydrogen, hydroxyl, –CN; or a –C_{1-6}alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, –C_{1-6}alkyl–C_{3-7}cycloalkyl, –C_{1-6}alkyl(C_{3-7}cycloalkyl)$_2$, –C_{1-6}alkyl-aryl, –C(O)–N(C_{0-6}alkyl)$_2$, –SO_naryl, –SO_n–C_{1-6}alkyl, –SO_n–C_{3-7}cycloalkyl, –SO_n–N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, –P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O) –O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –CH_2– or –O–; and

n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is –C_{1-6}alkyl, –cycloC_{3-6}alkyl, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently

a halogen, –OH, -CN, –C_1-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or -SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, –CN, or –C(O)–O–C_{0-6}alkyl, wherein the -C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF_3, –SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH

R5 is hydrogen, hydroxyl, –CN; or a –C_{1-6}alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, –C_{1-6}alkyl–C_{3-7}cycloalkyl, –C_{1-6}alkyl(C_{3-7}cycloalkyl)$_2$, –C_{1-6}alkyl-aryl, –C(O)–N(C_{0-6}alkyl)$_2$, –SO_naryl, –SO_n–C_{1-6}alkyl, –SO_n–C_{3-7}cycloalkyl, –SO_n–N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, –P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O) –O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –CH_2– or –O–; and

n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is $-C_{1\text{-}6}$alkyl, $-$cyclo$C_{3\text{-}6}$alkyl, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, $-$OH, -CN, $-C_1$-C_6alkyl, $-$C(O)(heterocyclo$C_{3\text{-}6}$alkyl), $-$C(O)$-$O$-$($C_{0\text{-}6}$alkyl), $-$C(O)$-$O$-$aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, $-$cyclo$C_{3\text{-}6}$alkyl, heterocyclo$C_{3\text{-}6}$alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or $-SO_n-$($C_{1\text{-}6}$alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, $-C_{1\text{-}6}$alkyl, or $-C_{1\text{-}6}$alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R_4 is hydrogen, halogen, $-$CN, phenyl, oxadiazolyl, or $-$C(O)$-$O$-C_{0\text{-}6}$alkyl, wherein the phenyl, oxadiazolyl, or $-$C(O)$-$O$-C_{0\text{-}6}$alkyl is optionally substituted with 1-3 independent halogen, CN, CF3,$-SO_n-C_{1\text{-}6}$alkyl, or $C_{1\text{-}6}$alkyl substituents, and the alkyl group is optionally substituted with OH

R5 is phenyl, pyridyl, or a 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, $-$CN, -CF3, $-C_{1\text{-}6}$alkyl, $-SO_n-C_{1\text{-}6}$alkyl, $-$C(O)$-$O$-C_{0\text{-}6}$alkyl, or hydroxy$C_{1\text{-}6}$alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form $-CH_2-$ or $-$O$-$; and

n is 0, 1, or 2.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-

tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "aryl" means an aromatic subsituent which is a single ring or multiple rings fused together. When formed of multiple rings, at least one of the constituent rings is aromatic. The preferred aryl substituents are phenyl and napthyl groups.

The term "cycloalkyloxy" unless specifically stated otherwise includes a cycloalkyl group connected by a short C_{1-2}alkyl length to the oxy connecting atom.

The term "C_{0-6}alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC_5alkyl is a five member ring containing from 5 to no carbon atoms. Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the aryl and the aryl groups are optionally substituted. If only one of the multiple moieties is

optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins,

procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) corticosteroids, iv) H1 receptor antagonists, v) beta 2 adrenoceptor agonists, vi) COX-2 selective inhibitors, vii) statins, viii) non-steroidal anti-inflammatory drugs ("NSAID"), and ix) M2/M3 antagonists. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Creams, ointments, jellies, solutions, or suspensions containing the compound of Formula I can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of conditions such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals,

diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues which are responsive to PDE4 inhibition, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01mg to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Further, it is understood that the PDE4 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as

granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules,

optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as PDE4 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues – maladies that are amenable to amelioration through inhibition of the PDE4 isoenzyme and the resulting elevated cCAMP levels – by the administration of an effective amount of the compounds of this invention. The term "mammals" includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than

humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the combinations of the PDE4 inhibiting compound of this invention can be advantageously used in combination with i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, or iii) M2/M3 antagonists.

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	1,1'-bi-2-naphthol
Bn	benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DAST	(diethylamino)sulfur trifluoride
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	triethylamine
GST	glutathione transferase
HMDS	hexamethyldisilazide
LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt $6H_2O$
Ms	methanesulfonyl = mesyl = SO_2Me
Ms0	methanesulfonate = mesylate

NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC	pyridinium chlorochromate
$Pd_2(dba)_3$	Bis(dibenzylideneacetone) palladium(0)
PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
r.t.	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO_2NH_2
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran
Thi	Thiophenediyl
TLC	thin layer chromatography
TMS-CN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
Tz	1H (or 2H)-tetrazol-5-yl
XANTPHOS	4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene
C_3H_5	Allyl

ALKYL GROUP ABBREVIATIONS

Me =	Methyl
Et =	ethyl
n-Pr =	normal propyl
i-Pr =	isopropyl
n-Bu =	normal butyl
i-Bu =	isobutyl
s-Bu =	secondary butyl
t-Bu =	tertiary butyl
c-Pr =	cyclopropyl
c-Bu =	cyclobutyl
c-Pen =	cyclopentyl
c-Hex =	cyclohexyl

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

LPS AND FMLP-INDUCED TNF-α AND LTB4 ASSAYS IN HUMAN WHOLE BLOOD

Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE4-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF-α and LTB4. Upon stimulation with LPS, activated monocytes express and secrete TNF-α up to 8 hours and plasma levels remain stable for 24 hours. Published studies have shown that inhibition of TNF-α by increasing intracellular cAMP via PDE4 inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB4 synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE4-selective inhibitors. As there is little LTB4 produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB4 synthesis by activated neutrophils. Thus, by using the same blood sample, it is possible to evaluate the potency of a compound on two surrogate markers of PDE4 activity in the whole blood by the following procedure.

Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. 500μL aliquots of blood were pre-incubated with either 2μL of vehicle (DMSO) or 2μL of test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10μL vehicle (PBS) as blanks or 10μL LPS (1μg/mL final concentration, #L-2630 (Sigma Chemical Co., St. Louis, MO) from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10μL of PBS (blank) or 10μL of LPS (1μg/mL final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10μL of PBS (blank) or 10μL of fMLP (1μM final concentration, #F-3506 (Sigma); diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at 4°C to obtain plasma. A 50μL aliquot of plasma was mixed with 200μL methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB_4 using an enzyme immunoassay kit (#520111 from Cayman Chemical Co., Ann Arbor, MI) according to the manufacturer's procedure. TNF-α was assayed in diluted plasma (in PBS) using an ELISA kit (Cistron Biotechnology, Pine Brook, NJ) according to manufacturer's procedure. The IC_{50} values of Examples 1-113 generally ranged from 0.02 μM to 26 μM.

ANTI-ALLERGIC ACTIVITY *IN VIVO*

Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs. Guinea pigs were initially sensitized to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminum hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later. At six weeks, animals were challenged with aerosolized ovalbumin while under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the

accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

SPA BASED PDE ACTIVITY ASSAY PROTOCOL

Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format as follows:

In a 96 well-plate at 30°C was added the test compound (dissolved in 2μL DMSO), 188mL of substrate buffer containing [2,8-^{3}H] adenosine 3',5'-cyclic phosphate (cAMP, 100nM to 50μM), 10mMmgCl$_2$, 1mM EDTA, 50mM Tris, pH 7.5. The reaction was initiated by the addition of 10mL of human recombinant PDE4 (the amount was controlled so that ~10% product was formed in 10min.). The reaction was stopped after 10min. by the addition of 1mg of PDE-SPA beads (Amersham Pharmacia Biotech, Inc., Piscataway, NJ). The product AMP generated was quantified on a Wallac Microbeta® 96-well plate counter (EG&G Wallac Co., Gaithersburg, MD). The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC$_{50}$ value was approximated with a non-linear regression fit using the standard 4-parameter/multiple binding sites equation from a ten point titration.

The IC$_{50}$ values of Examples 1-113 were determined with 100nM cAMP using the purified GST fusion protein of the human recombinant phosphodiesterase IVa (met-248) produced from a baculovirus/Sf-9 expression system. The IC$_{50}$ values of Examples 1-113 generally ranged from 0.1 nM to 25 nM.

The examples that follow are intended as an illustration of certain preferred embodiments of the invention and no limitation of the invention is implied.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or ambient temperature - that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates

decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. Yields are given for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)),mL (milliliters), g (gram(s)),mg (milligrams(s)), mol (moles),mmol (millimoles), eq (equivalent(s)).

Methods of Synthesis

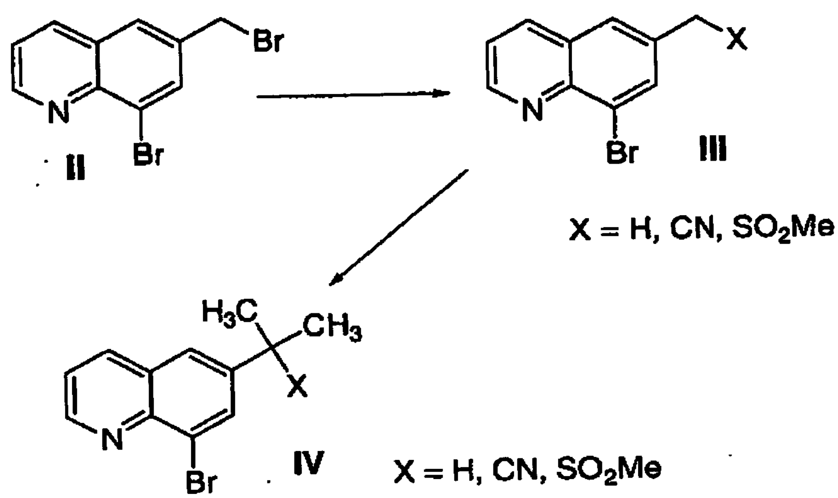
Compounds of the present invention can be prepared according to the following methods. The substituents are the same as in Formula I except where defined otherwise.

Scheme 1:
Preparation of 8-bromo-quinolines

The quinolines of formula IV may be obtained from literature procedure (R.H.F. Manske and M.Kulka, "The Skraup Synthesis of Quinolines"; Org. Reaction, vol. 7, p. 59-98, 1953 or in International Patent Publication WO 94/22852) or prepared in a multi-step sequence from the requisite 8-bromo-6-methyl-quinoline **II**. Treatment of 8-bromo-6-methyl-quinoline (from references cited in text) with brominating agents such as NBS in solvents such as chlorobenzene in presence of radical initiator such as AIBN or benzoyl peroxide provide the 8-bromo-6-bromomethyl-quinoline **II**. The primary bromide can be displace by nucleophiles such as sodium methanesulfinate or potassium cyanide in a solvent such as DMF. Two sequential alkylation using alkylating agents such as iodomethane and a base

such as potassium t-butoxide in a solvent such as THF can yields 8-bromo-quinolines of such as **IV**.

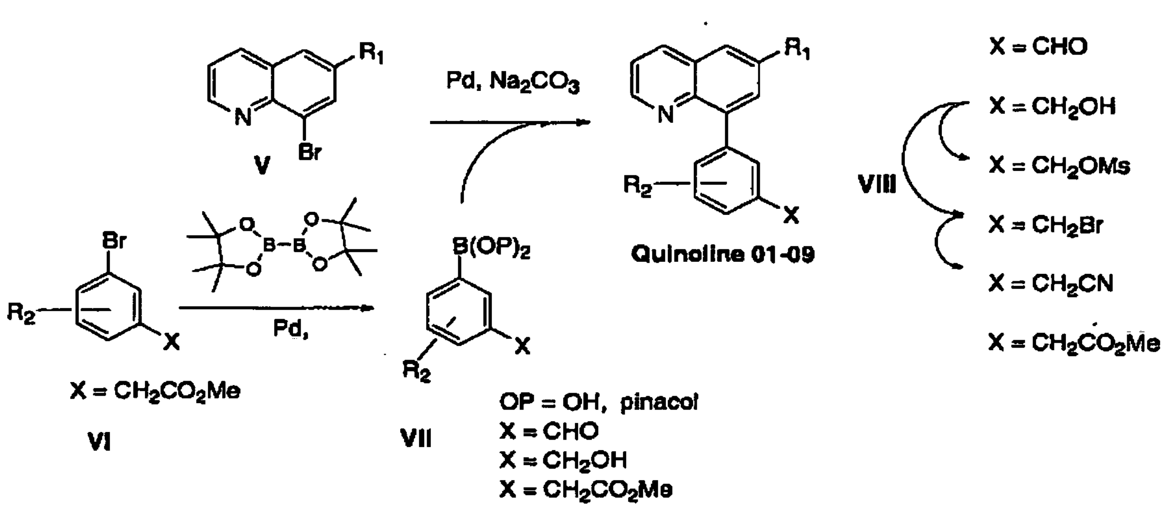
Scheme 1



Scheme 2:
Preparation of 8-Aryl-quinolines

The 8-aryl-quinolines of the formula **VIII** may be prepared by coupling the 8-bromo-quinoline such as **V** with appropriately substituted phenyl-boronic acids or esters such as **VII** with heating in the presence of various palladium catalyst such as $Pd(Ph_3P)_4$ and a base such as sodium carbonate in a mixture of solvent such as DME-H_2O. The alcohol **VIII** X = CH_2OH) may be converted to the bromide by treatment with HBr (aq.) in a solvent such as acetic acid or to the mesylate and then to the cyanide derivatives using standard organic chemistry protocols.

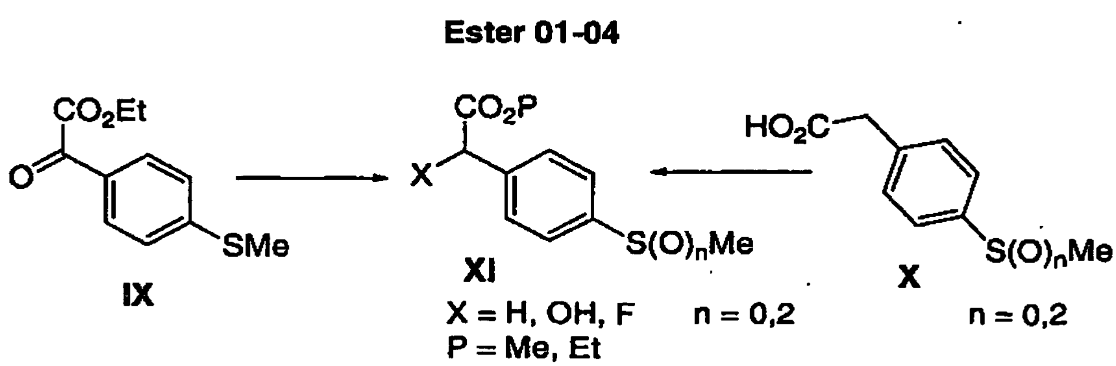
Scheme 2



Scheme 3:
Preparation of phenyl acetic acid derivatives

The phenyl acetic acid derivatives **XI** may be prepared from esterification of commercial product such as **X** using diazomethane for example or by reduction of alpha-keto analog **IX** (*J. Med. Chem.*, 24:399(1981)) using hydride such as $NaBH_4$ in a solvent such as ethanol. The alcohol **XI** (X = OH) can be transformed into **XI** (X = F) using DAST (*J. Org. Chem.*, 40:574(1975)) or other commercial equivalents. Sulfur atom may also be oxidized to sulfone by oxidizing agent such as oxone in a mixture of solvents such as THF/MeOH/H_2O.

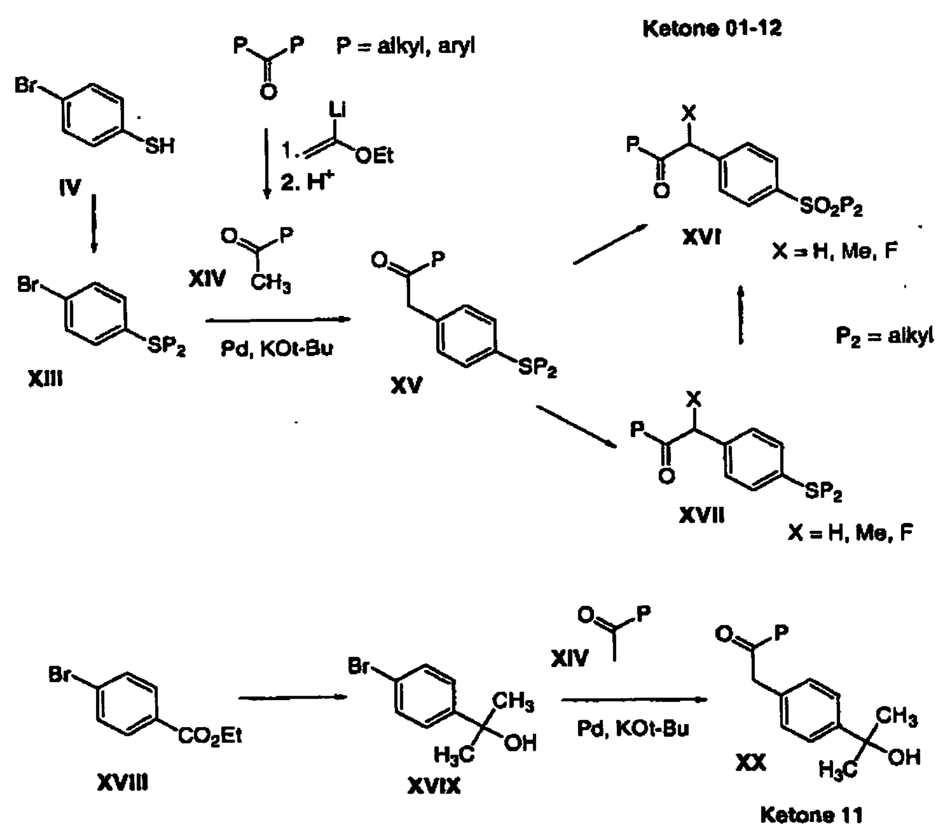
Scheme 3



Scheme 4:
Preparation of phenyl ethanone derivatives

Phenyl-ethanone intermediate like **XX** or **XV** may be prepared from appropriately substituted aryl bromide and a methylketone using as a catalysis such as $Pd_2(dba)_3$ with ligands such as xanphos or binap in a solvent like THF with a base such sodium tert-butoxide. Methyl ketone such as **XIV** can be obtained from commercial sources or prepared from condensation of ethyl vinyl ether lithium salt onto ketone such as 3-pentanone followed by hydrolysis in acidic media. Aryl bromide such as **XIII** or **XVIX** can be prepared using standard organic chemistry protocols. Further modifications of phenyl-ethanone such as **XV** will lead to substituted ethanone **XVI** and **XVII** by alkylation with alkyl idodide such as methyl iodide or a fluoride source such as N-fluorobenzenesulfonimide (*Synlett*, 187, (1991)) and a base such as potassium tert-butoxide.

Scheme 4

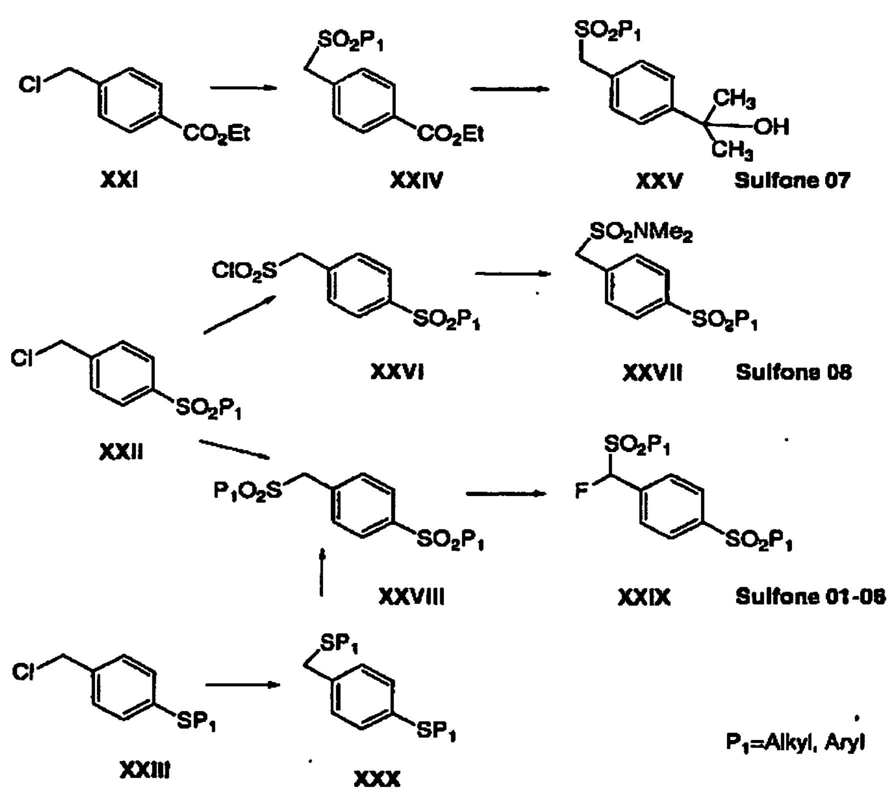


Scheme 5:

Preparation of sulfonylmethyl-phenyl derivatives

Sulfonylmethyl phenyl intermediate like **XXIV** to **XXX** may be prepared from appropriately substituted benzyl halide by displacement of halide by nucleophiles such as methanesulfinic acid sodium salt in a solvent such as DMF. Alternatively, alkyl and aryl thiols can displace the benzylic halide with a base such as cesium carbonate in a solvent such as DMF. Oxidation of sulfide such as **XXX** with oxidizing agents such as oxone will lead to sulfone derivatives such as **XXVIII.** Displacement of the benzylic halide with sulfur followed by oxidation with Cl_2 for example will afford the corresponding sulfonyl chloride such as **XXVI.** Further condensation with nucleophiles such as amines in a solvent like dichloromethane will give sulfonimides such as **XVII.** Those methylsulfone **XV** to **XVIII** can also be alkylated with a fluoride source such as N-fluorobenzenesulfonimide (*Synlett*, 187, (1991)) and a base such as potassium tert-butoxide to give alpha fluoro analogs such as **XXIX.**

Scheme 5

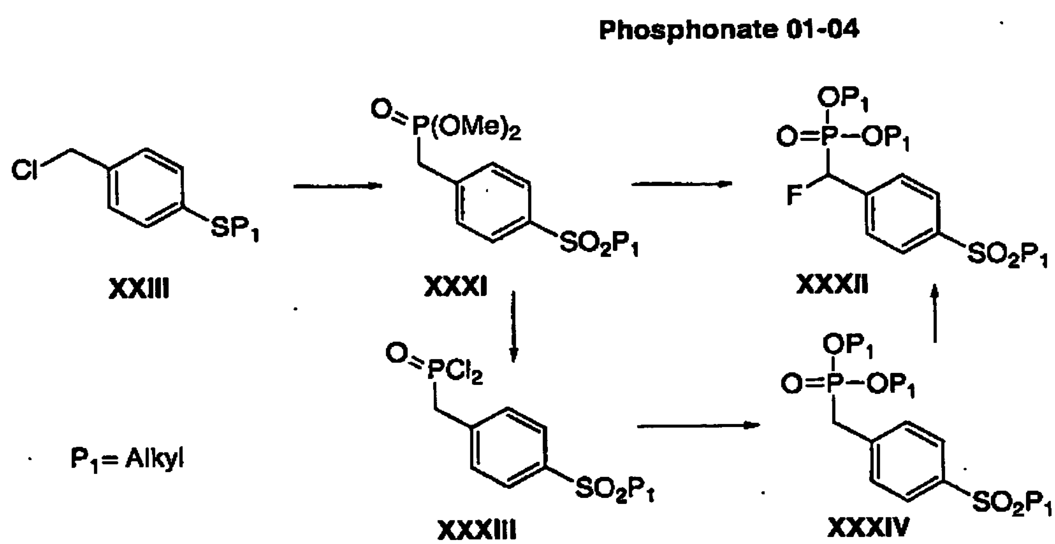


Scheme 6:

Preparation of phosphonylmethyl-phenyl derivatives

Phosphonylmethyl phenyl intermediate like **XXXI** to **XXXIV** may be prepared from appropriately substituted benzyl halide by displacement of halide by nucleophiles such as trimethylphosphite. Hydrolysis to phosphonic acid may be accomplished using TMSBr in a solvent such as chloroform. Conversion to the acid chloride using oxalyl chloride for example in a solvent such as dichloromethane will provide the starting material for further condensation with nucleophiles such as alcohol in a solvent like dichloromethane and with a base such as triethylamine to give various phosphonate esters such as **XXXIV**. The latter can also be alkylated with a fluoride source such as N-fluorobenzenesulfonimide (*Synlett*, 187, (1991)) and a base such as potassium tert-butoxide to give alpha fluoro analogs such as **XXXII**.

Scheme 6

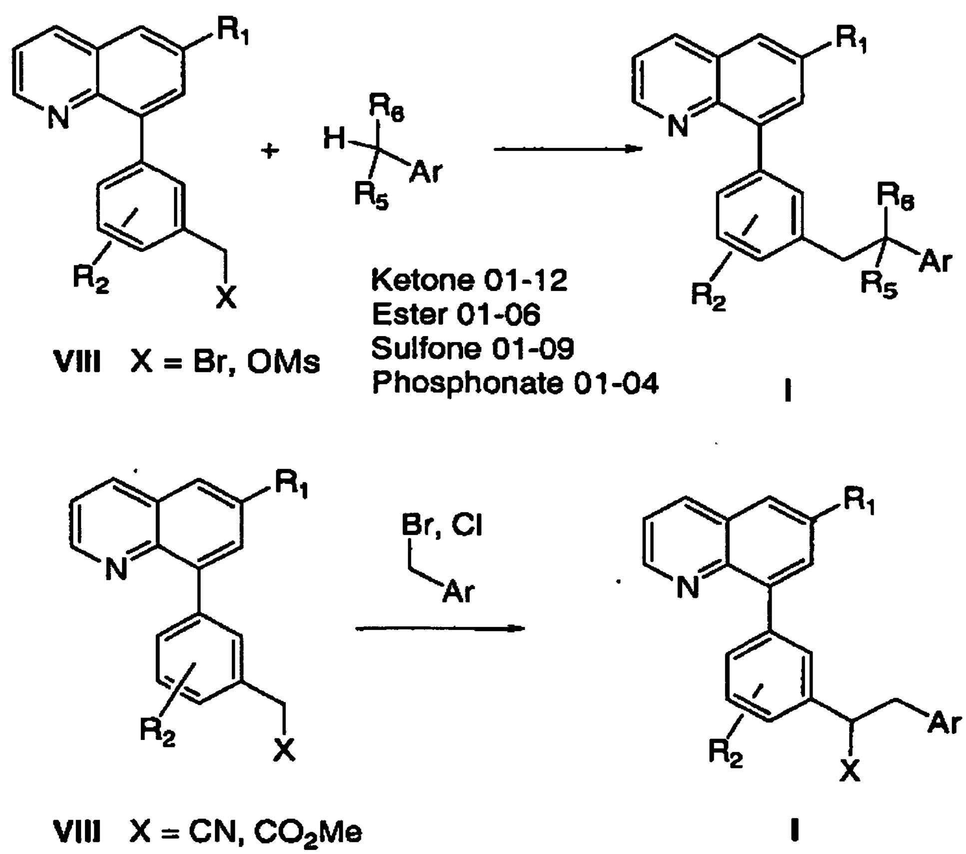


Scheme 7:

Preparation of quinoline of formula I

The quinolines of formula **I** may be obtained from alkylation of various carbonyl containing intermediates from **Schemes 3** to **6** (esters, ketones, aldehydes, sulfonyl or phosphonates) with appropriate electrophile derivatives (**Scheme 2**). For example, the treatment of an intermediate (containing an acidic proton like a ketone etc..) with a base such as potassium t-butoxide in a organic solvent such THF, followed by quenching with an electrophile such as bromomethyl quinoline **VIII**, ($X=CH_2Br$) will give desired product of formula **I**. Alternatively, the quinoline / electrophile can be reverse to a quinoline / nucleophile and coupling with aryl halide will afford compounds with a different substitution pattern as described in **Scheme 7**.

Scheme 7

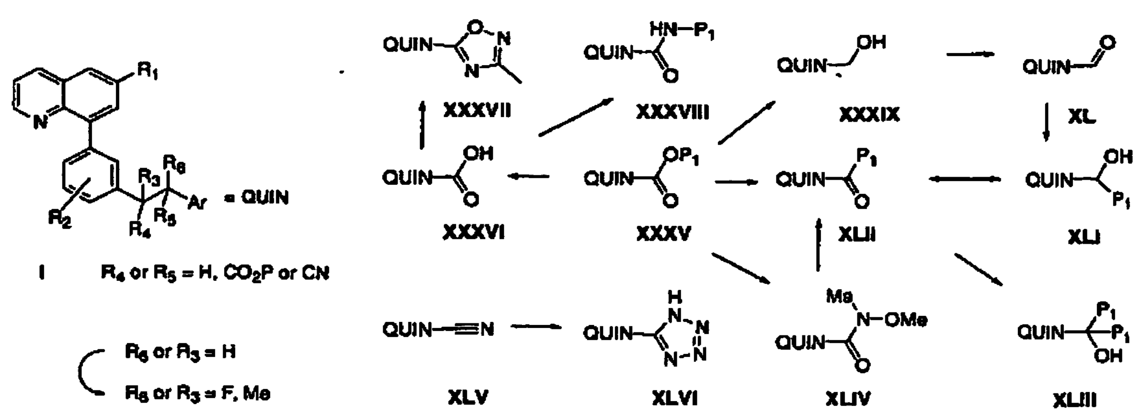


Scheme 8:

Preparation of carboxylic acid derived analogs

Quinoline of formula I containing a carboxylic acid derivative such as **XXXV** can serve as a starting material for various other analogs as exemplified in **Scheme 8**. Formation of oxadiazole **XXXVII** may be achieved by activation of acetic acid **XXXVI** with EDCI in a solvent such as diglyme followed by the addition of N-hydroxy-acetamidine and subsequent heating of the reaction mixture. Formation of the acid chloride or activation of acid by using standard procedures followed by addition of amines produces amide **XXXVIII**. Tetrazole like **XXXXVI** can be obtained from nitrile **XXXXV** by heating with tributyltin azide in a solvent such as xylene. All other derivatives described in scheme 8 can be obtained using standard organic synthesis procedures related to reduction and addition of nucleophiles such as lithium or magnesium salts to the carbonyl functional group. Those standards procedure also includes oxidation of alcohol to ketone and transformation of ester to Weinred type amide. All analogs containing a acidic proton at the benzilic position, can also be alkylated with a fluoride source such as N-fluorobenzenesulfonimide (*Synlett*, 187, (1991)) or alkyl halide such as methyl iodide and a base such as potassium tert-butoxide to give alpha fluoro analogs such as I (R_6 = F or Me).

Scheme 8



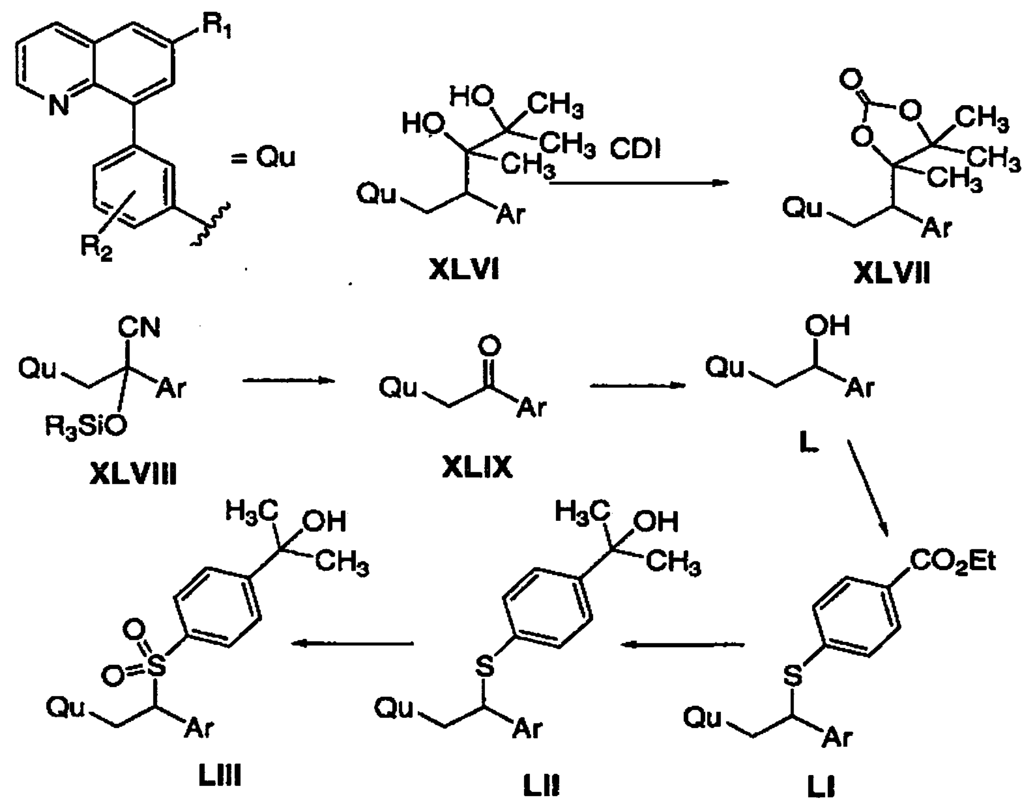
P_1= Alkyl, Aryl

Scheme 9:

Preparation of derivatives of quinoline of formula I

Alternatively, derivatives of formula I containing a masked carbonyl function in the form of a cyanohydrin of type **XLVIII** can be treated with tetra-butylammonium fluoride in a solvent such as THF to give the ketone **XLIX**. Reduction of the carbonyl function with an hydride source such as sodium borohydride in a solvent such as methanol provides the secondary alcohol **L**. Mitsunubo type displacement of the benzylic alcohol with appropriate nucleophiles such as a substituted thiophenol will give the corresponding thio ether **LI**. Further manipulation of ester function to the tertiary alcohol and oxidation of sulfur to sulfone with an oxidizing agent such as oxone in a solvent such a mixture of THF/MeOH/H_2O gives **LIII**. 1,2-Diols like **XLVI** can be cyclized to carbonate **XLVII** using, for example, carbonyl diimidazole and heating.

Scheme 9

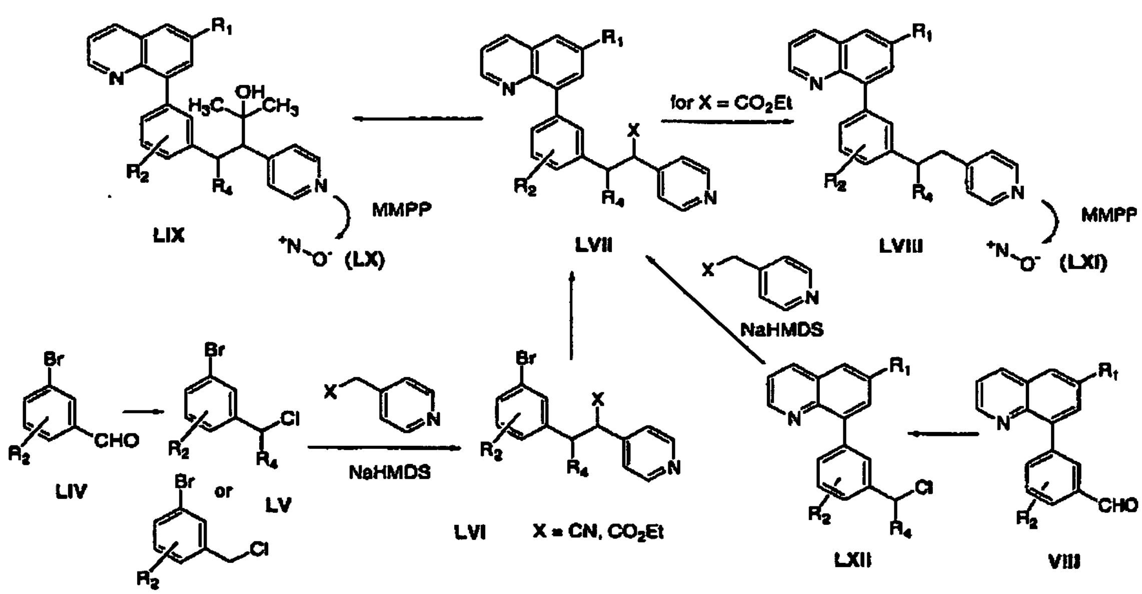


Scheme 10:

Preparation of 4-pyridinyl derivatives of quinoline of formula I

Another synthetic approaches to quinoline of formula I is derived from custom made or commercial 3-bromobenzyl halides like **LV**. The latter can be derived from appropriately substituted benzaldehyde by addition of alkyl or arylmagnesium or lithium salts followed by conversion of the corresponding alcohol to the halide by using thionyl chloride, for example, in a solvent such as benzene. 4-Pyridinyl acetate or 4-pyridinyl acetonitrile can be deprotonated using a base such as NaHMDS and then alkylated with the benzylic halide **LV** or benzyl halide derived from quinoline **VIII (Scheme 2)**. The derivatives of type **LVII**, with an ester functional group, can be hydrolyzed and decarboxylated to **LVIII** using an aqueous base such as NaOH followed by an acidic work-up. Alternatively, treatment of **LVII** with a nucleophiles like methylmagnesium bromide for example, can produce tertiary alcohol like **LIX**. Other functional group manipulation from an ester was described in **Scheme 8**. The pyridinyl can be oxidized to the pyridinyl N-oxide with an oxidizing agent such as MMPP in a solvent such a mixture of CH_2Cl_2/MeOH to gives **LX** or **LXI**.

Scheme 10

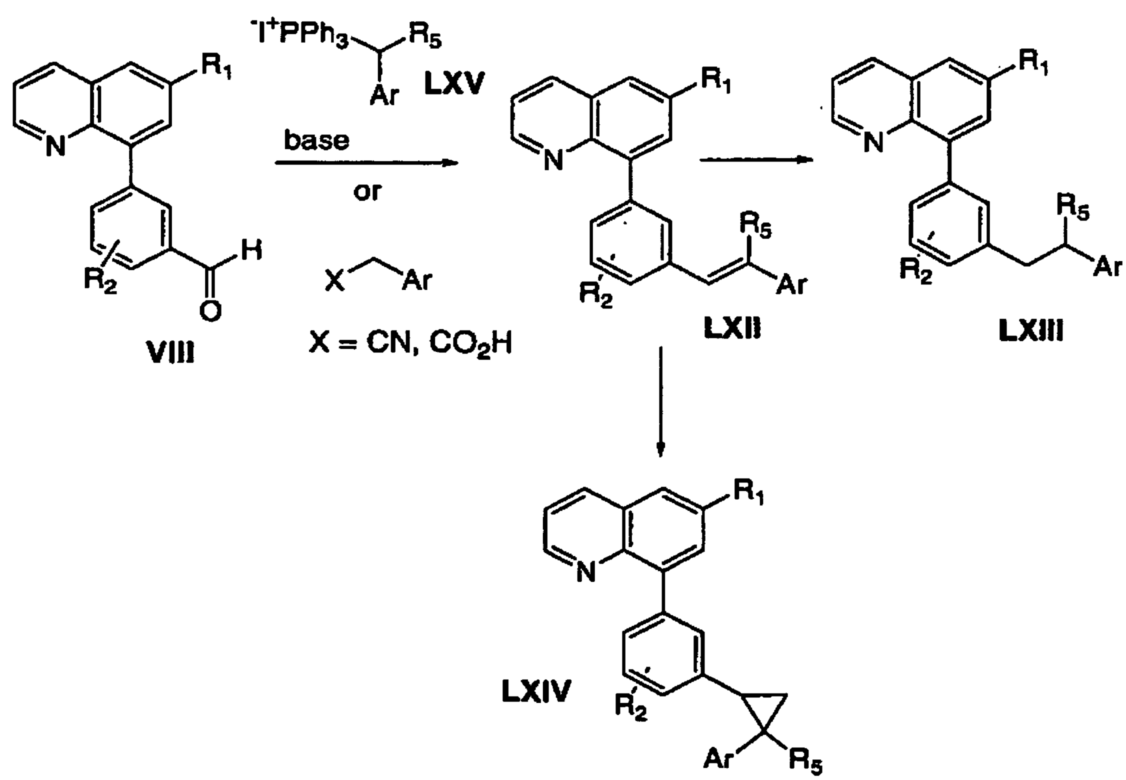


Scheme 11:

Preparation of stilbene derivatives of quinoline of formula I

Intermediate such as **LXII** - containing a double bond can serve as a precursor to compound of formula **I**. Condensation of aldehydes **VIII** with substituted acetic acid or acetonitrile and a base such as piperidine and heating will provide **LXII**. Alternatively, phosphonium salts **LXV** with a base such as potassium tert-butoxide in a solvent such as THF can react with aldehyde of formula **VIII**. Reduction of the olefin using catalyst such as palladium on carbon in a solvent such as THF/MeOH under hydrogen atmosphere or polymer supported phenylhydrazide in a solvent such as toluene with heating will provide compound like **LXIII**. Cyclopropanation of the double bond using trimethyl-sulfoxonium iodide and a base such as NaH in a solvent such as DMSO will give derivatives of formula **LXIV**.

Scheme 11

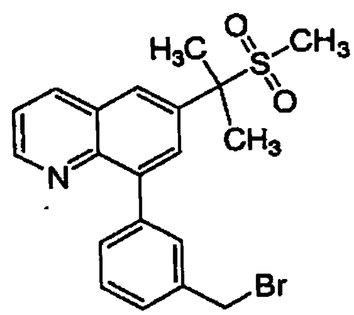


PREPARATION OF INTERMEDIATES

PREPARATION OF QUINOLINES

Quinoline 01

8-(3-Bromomethyl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



Step 1: 8-Bromo-6-methanesulfonylmethyl-quinoline

To a solution of 6-bromomethyl-8-bromoquinoline (60g, 200mmol, described in International Patent Publication WO 94/22852) in DMF (500mL) was added sodium methanesulfinate (27.6g, 270mmol). After stirring overnight at 21°C, the mixture was quenched with H_2O (2L), stirred for 1h, isolated by filtration, and washed with Et_2O to yield the 8-Bromo-6-methanesulfonylmethyl-quinoline as a white solid.

Step 2: 8-Bromo-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

To a solution of the 8-Bromo-6-methanesulfonylmethyl-quinoline from Step 1 above (60g, 200mmol) in THF (2L) at 0°C (internal), was added potassium *t*-butoxide (260mL, 1M, THF) over 30min. After 0.5h at 0°C, MeI (20mL, 320mmol) was added and the resulting reaction mixture stirred at 0°C for 2h. More potassium *t*-butoxide (200mL, 1M, THF) was then added over 30min, followed by MeI (20mL, 320mmol), and the mixture stirred at rt for 2h. The mixture was neutralised with saturated NH_4Cl solution and extracted with EtOAc. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Stirring the solid in ether, followed by filtration gave the 8-Bromo-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline as a pale yellow solid.

Step 3: {3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol

A mixture of the 8-Bromo-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from Step 2 above (26g, 79mmol), 3-(hydroxymethyl) phenyl-boronic acid (14g, 92mmol), sodium carbonate (120mL, 2M, H_2O), $PdCl_2(Ph_3P)_2$ (2g) in DME (300mL) was heated at 90-100°C for 8h. The resulting reaction mixture was filtered on a large plug/column of silica gel and the eluted with EtOAc. The organic extracts were concentrated and the resulting suspension diluted with Et_2O and stirred vigorously for 3h. The desired {3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol was isolated as a white solid by filtration.

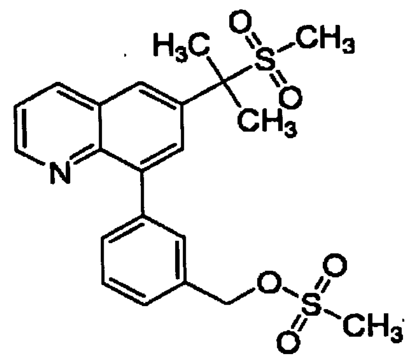
Step 4: 8-(3-Bromomethyl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

A suspension of the {3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol compound from Step 3 above (30g, 85mmol) in AcOH (140mL) and HBr (48mL, 48% aq) was stirred for 18h at 80°C. The resulting mixture was cooled to 0°C and poured into 2L of cold NaOH (0.3N). The pH of the resulting solution was adjusted to 5 and filtered. The resulting solid was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution, brine, dried ($MgSO_4$), filtered and concentrated. Stirring the solid in ether/ EtOAc, followed by filtration gave desired

8-(3-Bromomethyl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline as a pale brown solid.

Quinoline 02

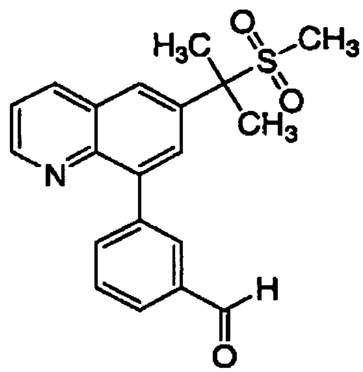
{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol O-methanesulfonate



To a solution of the alcohol from **Quinoline 01, Step 3** (5.15g, 17mmol) in CH_2Cl_2 (150mL) at -78°C was added Et_3N (3.6mL, 26mmol) and methanesulfonyl chloride (1.6mL, 21mmol). After 0.5h at-78°C, the mixture was neutralized with saturated NH_4Cl solution, diluted with water, and extracted with ether. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield the title compound as a white foam.

Quinoline 03

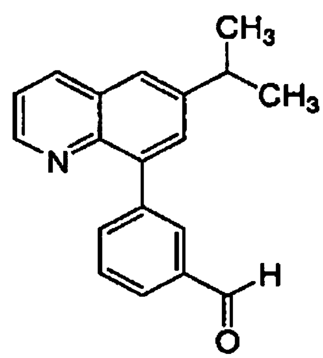
3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-benzaldehyde



Following the procedures described in **Quinoline 01, Steps 1-3**, but substituting 3-formylphenyl-boronic acid for 3-(hydroxymethyl)-phenyl-boronic acid in **Step 3**, the title compound was obtained as pale yellow solid.

Quinoline 04

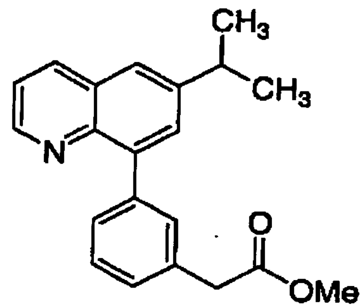
3-(6-Isopropyl-quinolin-8-yl)-benzaldehyde



A mixture of 8-bromo-6-isopropyl-quinoline (9.79g, 39mmol, described in International Patent Publication WO 94/22852), 3-(formyl)-phenyl-boronic acid (11.7g, 78mmol), sodium carbonate (78mL, 2M, H_2O), $Pd(Ph_3P)_4$ (2.7g, 2.3mmol) in DME (200mL) was heated at 70°C for 18h. The reaction mixture was cooled to 21°C then diluted with water and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20) provided the title compound.

Quinoline 05

[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetic acid methyl ester



Step 1: (3-Bromo-phenyl)-acetic acid methyl ester

To a solution of 3-bromophenylacetic acid (10g, 46mmol) in CH_2Cl_2 (20mL) was added CH_2N_2 (Et_2O) until yellow coloration persisted. The resulting reaction mixture was quenched with AcOH, and diluted with a $NaHCO_3$ solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated to provided the (3-Bromo-phenyl)-acetic acid methyl ester compound.

Step 2: [3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester

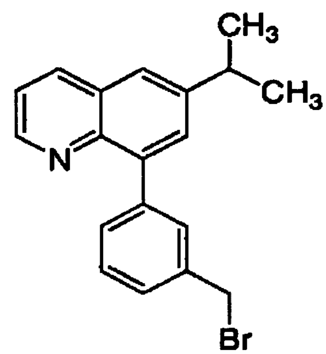
A solution of (3-Bromo-phenyl)-acetic acid methyl ester from **Step 1** (10.9mg, 48mmol), diboron pinacol ester (14.5g, 57mmol), KOAc (16.33g, 166mmol) and $PdCl_2$(dppf) (1.94g, 2.38mmol) in DMF (250mL) was heated at 80°C under N_2 for 3h. The resulting reaction mixture was cooled to 21°C and diluted with water and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 65:35) provided the [3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester compound.

Step 3: [3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetic acid methyl ester

A solution of [3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester from **Step 2** (4g, 14mmol), 8-bromo-6-isopropylquinoline (3g, 12mmol), Na_2CO_3 (2M, 18mL, 36mmol) and $Pd(PPh_3)_4$ (692mg, 0.6mmol) in DMF (250mL) was heated at 80°C under N_2 for 18h. The resulting reaction mixture was cooled to 21°C and diluted with water and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20) provided the [3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetic acid methyl ester compound.

Quinoline 06

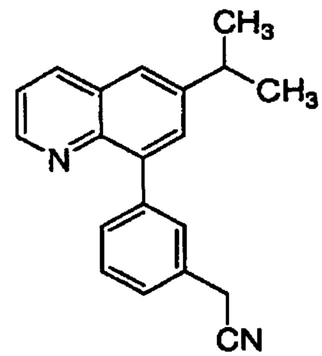
8-(3-Bromomethyl-phenyl)-6-isopropyl-quinoline



Quinoline 06 was prepared according to the procedure described in **Quinoline 01, Steps 3** and **4**, but 6-isopropyl-8-bromo-quinoline was used as the starting material. Flash chromatography (hexane/EtOAc) afforded the title compound as a yellow solid.

Quinoline 07

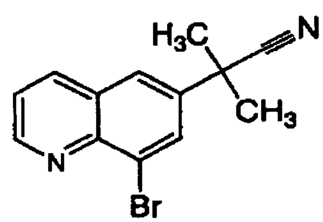
[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetonitrile



To a solution of **Quinoline 06** (1.0g, 2.94mmol) in CH_3CN (15mL) was added KCN (244mg, 3.74mmol) and 18-crown-6 (100mg, 0.37mmol). The resulting reaction mixture was stirred 18h at 80°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 75:25) provided the title compound.

Quinoline 08

2-(8-Bromo-quinolin-6-yl)-2-methyl-propionitrile



Step 1: (8-Bromo-quinolin-6-yl)-acetonitrile

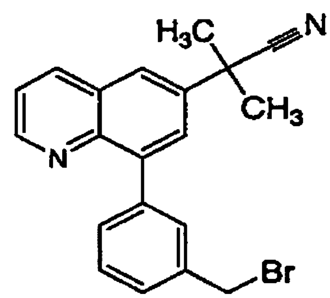
DMF (10mL) and H_2O (5mL) were added to 6-bromomethyl-8-bromoquinoline (3g) (described in International Patent Publication WO 94/22852) and potassium cyanide (1.6g). After heating at 100°C for 1 hour, the resulting mixture was quenched with H_2O (100mL) and extracted with EtOAc. The combined organic extracts were washed with water (3x), brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane:EtOAc, 3:1) yielded the (8-Bromo-quinolin-6-yl)-acetonitrile compound as a white solid.

Step 2: 2-(8-Bromo-quinolin-6-yl)-2-methyl-propionitrile

To a solution of (8-Bromo-quinolin-6-yl)-acetonitrile from **Step 1** (3g, 12.1mmol) in THF (100mL) at -78°C, was added MeI (1.7mL, 27mmol) followed by potassium *t*-butoxide (27mL, 27mmol). After 2h at -78°C, the resulting mixture was warmed to 0°C, was poured in saturated aqueous NH_4Cl, then extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane:EtOAc, 3:1) afforded the 2-(8-Bromo-quinolin-6-yl)-2-methyl-propionitrile as a white solid.

Quinoline 09

2-[8-(3-Bromomethyl-phenyl)-quinolin-6-yl]-2-methyl-propionitrile

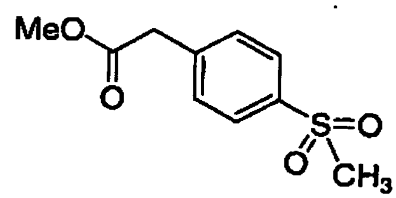


Quinoline 09 was prepared according to the procedure described above in **Quinoline 01, Steps 3** and **4** but used **Quinoline 08** as the starting material. Flash chromatography (hexane/EtOAc) afforded the title compound as a yellow solid.

PREPARATIONS OF ESTERS

Ester 01

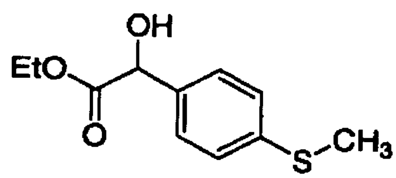
(4-Methanesulfonyl-phenyl)-acetic acid methyl ester



(4-Methanesulfonyl-phenyl)-acetic acid was treated with an etheral solution of diazomethane until completion of esterification by TLC. The solvent was evaporated, the residue triturated in hexane/ether and filtered to afford the title compound as a white solid.

Ester 02

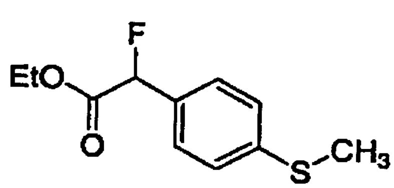
Hydroxy-(4-methylsulfanyl-phenyl)-acetic acid ethyl ester



To a solution of ethyl α-oxo 4-methylthiophenylacetate (obtained from thioanisole and ethyl oxalyl chloride using procedure described in *J. Med. Chem.*, p.403(1981) (30g, 134mmol) in EtOH at -78°C, was added $NaBH_4$ (2.5g, 66mmol) portionwise. After 40min at -78°C, the resulting reaction mixture was quenched by slow addition of a saturated ammonium chloride solution, allowed to warm to 21°C, poured into water (0.5L) and stirred for 2h. The suspension was filtered to provide the title compound as a white solid.

Ester 03

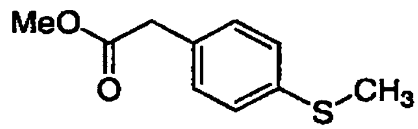
Fluoro-(4-methylsulfanyl-phenyl)-acetic acid ethyl ester



To a solution of **Ester 02** (10.9g, 48mmol) in CH_2Cl_2 (300mL) at-78°C was added [bis(2-methoxyethyl)amino]sulfur trifluoride (10mL, 54mmol) dropwise. The resulting reaction mixture was warmed slowly to 10°C, then poured into an ether/$NaHCO_3$ solution. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 95:5) provided the title compound as an oil.

Ester 04

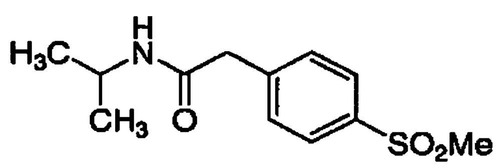
(4-Methylsulfanyl-phenyl)-acetic acid methyl ester



(4-Methylsulfanyl-phenyl)-acetic acid was treated with an etheral solution of diazomethane until completion of esterification. The solvent was evaporated, the residue triturated in hexane/ether, and filtered to afford the title compound as a white solid.

Ester 05

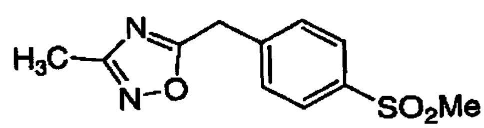
N-Isopropyl-2-(4-methanesulfonyl-phenyl)-acetamide



To a solution of (4-methanesulfonyl-phenyl)-acetic acid (2.5g, 11.7mmol) in CH_2Cl_2 (20mL) was added EDCI (2.46g, 12.9mmol) followed by diisopropyl amine (1.2mL) and DMAP (140mg, 1.2mmol). After 18h at 21°C, the resulting reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate/THF, 35:60:5) provided the title compound as a white solid.

Ester 06

5-(4-Methanesulfonyl-benzyl)-3-methyl-[1,2,4]oxadiazole

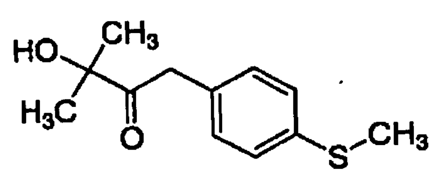


Ester 06 prepared according to the procedure described in **Example 83** but using (4-methanesulfonyl-phenyl)-acetic acid as the starting material. Flash chromatography (hexane/EtOAc) afforded the title compound as a yellow solid.

PREPARATION OF KETONES

Ketone 01

3-Hydroxy-3-methyl-1-(4-methylsulfanyl-phenyl)-butan-2-one

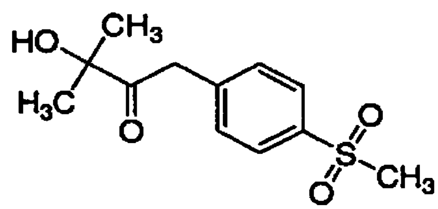


To a solution of sodium *tert*-butoxide (12g, 125mmol), XANTPHOS (2.05g, 3.5mmol) and $Pd_2(dba)_3$ (1.35g, 1.5mmol) in THF (600mL) was added 4-bromothioanisole (20g, 98mmol) and 3-hydroxy-3-methyl-butan-2-one (12g,

117mmol). The resulting reaction mixture was heated to 75°C for 2h then cooled to r.t. and diluted with water. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 85:15-80:20) provided the title compound as a pale brown solid.

Ketone 02

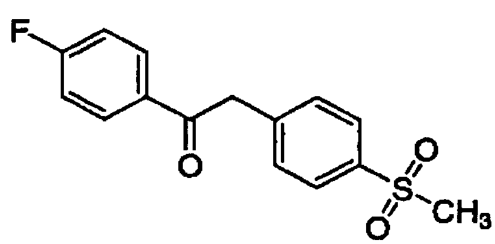
3-Hydroxy-1-(4-methanesulfonyl-phenyl)-3-methyl-butan-2-one



To a solution of **Ketone 01** (10.7g, 48mmol) in THF/MeOH (2:1, 375mL) was added OXONE® (60g, 98mmol) followed by water (slowly, 125mL). After 2h, the reaction mixture was diluted with ether and a saturated $NaHCO_3$ solution. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by stirring vigorously in hexane/ether and isolation by filtration gave the desired product as a pale yellow solid (8.3g).

Ketone 03

1-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-ethanone



Step 1: 1-(4-Fluoro-phenyl)-2-(4-methylsulfanyl-phenyl)-ethanone

To a solution of sodium *tert*-butoxide (480mg, 5mmol), BINAP (racemic, 112mg, 0.18mmol) and $Pd_2(dba)_3$ (68mg, 0.075mmol) in THF (10mL) was

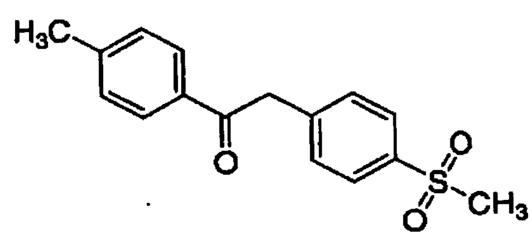
added 4-bromo-thioanisole (914mg, 4.5mmol) and 4-fluoro-acetophenone (690mg, 5mmol). The resulting reaction mixture was heated to 80°C for 3h then cooled to 21°C and diluted with water. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 8:2) provided the 1-(4-Fluoro-phenyl)-2-(4-methylsulfanyl-phenyl)-ethanone compound as a solid after precipitation in ether/ethyl acetate.

Step 2: 1-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-ethanone

Following the procedures described in **Ketone 02** but substituting 1-(4-fluoro-phenyl)-2-(4-methylsulfanyl-phenyl)-ethanone for **Ketone 01**, the 1-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-ethanone compound was obtained as a white solid.

Ketone 04

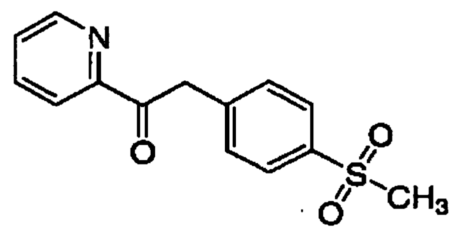
2-(4-Methanesulfonyl-phenyl)-1-p-tolyl-ethanone



Following the procedures described in **Ketone 03**, but substituting 4-methyl-acetophenone for 4-fluoro-acetophenone, the title compound was obtained as a white solid.

Ketone 05

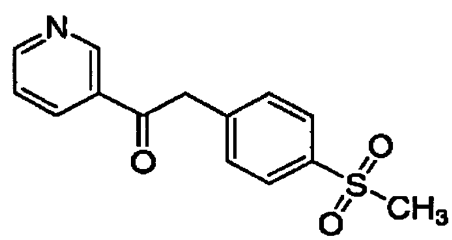
2-(4-Methanesulfonyl-phenyl)-1-pyridin-2-yl-ethanone



Following the procedures described in **Ketone 03**, but substituting 2-acetylpyridine for 4-fluoroacetophenone, the title compound was obtained as a beige solid.

Ketone 06

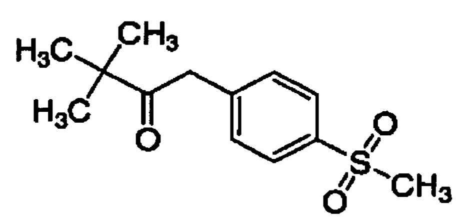
2-(4-Methanesulfonyl-phenyl)-1-pyridin-3-yl-ethanone



Following the procedures described in **Ketone 03**, but substituting 3-acetyl-pyridine for 4-fluoro-acetophenone, the title compound was obtained.

Ketone 07

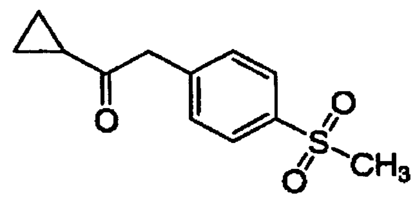
1-(4-Methanesulfonyl-phenyl)-3,3-dimethyl-butan-2-one



Following the procedures described in **Ketone 03**, but substituting pinacolone for 4-fluoroacetophenone, the title compound was obtained as a white solid.

Ketone 08

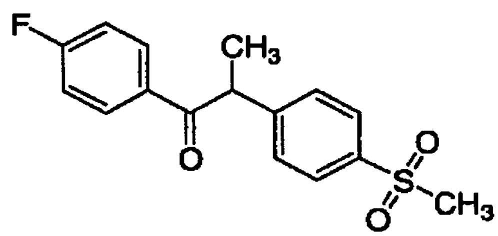
1-Cyclopropyl-2-(4-methanesulfonyl-phenyl)-ethanone



Following the procedures described in **Ketone 01** and **Ketone 02**, but substituting 1-cyclopropyl-ethanone for 3-hydroxy-3-methyl-butan-2-one, the title compound was obtained.

Ketone 09

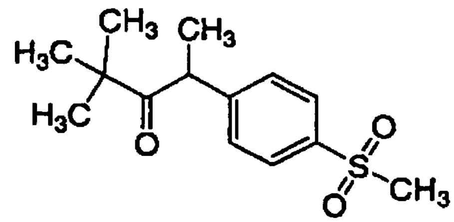
1-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-propan-1-one



To a solution of **Ketone 03** (240mg, 0.822mmol) in THF (8mL) at -30°C was added potassium tert-butoxide (1M, THF, 0.9mL, 0.9mmol) dropwise. After 20min, iodomethane (0.076mL, 1.22mmol) was added and the resulting reaction mixture was stirred for 2h at -20°C, and then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 95:5) provided the title compound.

Ketone 10

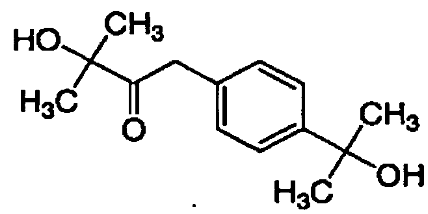
4-(4-Methanesulfonyl-phenyl)-2,2-dimethyl-pentan-3-one



Following the procedures described in **Ketone 01**, but substituting pinacolone for 3-hydroxy-3-methyl-butan-2-one, followed by the procedures described in **Ketone 09** and finally using procedures described in **Ketone 02**, the title compound was obtained.

Ketone 11

3-Hydroxy-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-methyl-butan-2-one



Step 1: 2-(4-Bromo-phenyl)-propan-2-ol

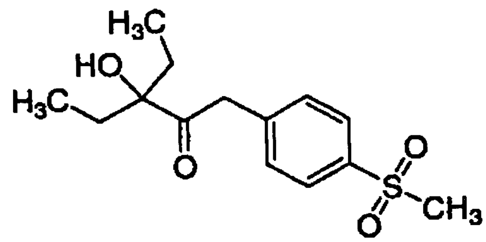
Following the procedures described in **Example 24**, but substituting ethyl 4-bromobenzoate for **Example 07**, the 2-(4-bromo-phenyl)-propan-2-ol compound was obtained as a white solid.

Step 2: 3-Hydroxy-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-methyl-butan-2-one

Following the procedures described in **Ketone 01**, but substituting 2-(4-bromophenyl)-2-propanol for 4-bromothioanisole, the 3-hydroxy-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-methyl-butan-2-one compound was obtained as an oil.

Ketone 12

3-Ethyl-3-hydroxy-1-(4-methanesulfonyl-phenyl)-pentan-2-one



Step 1: 3-Ethyl-3-hydroxy-pentan-2-one

To a solution of ethyl vinylether (10mL, 104mmol) in THF (50mL) at -78°C was added tert-BuLi (1.7M, pentane, 45mL, 76mmol) dropwise. The mixture was stirred at -10°C for 15min then cooled to -78°C and 3-pentanone (5.0g, 58mmol, in 5mL of THF) was added dropwise. The resulting reaction mixture was allowed to warm slowly to 21°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extract was stirred with 6mL of HCl 2% for 18h then washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (eluting with hexane/ethyl acetate, 95:5) to provide the 3-ethyl-3-hydroxy-pentan-2-one compound as an oil.

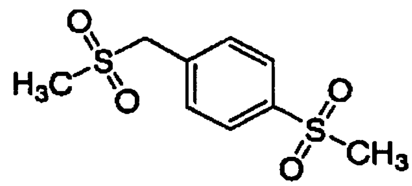
Step 2: 3-Ethyl-3-hydroxy-1-(4-methanesulfonyl-phenyl)-pentan-2-one

Following the procedures described in **Ketone 01** then in **Ketone 02**, but substituting 3-ethyl-3-hydroxy-pentan-2-one for 3-hydroxy-3-methyl-butan-2-one. Purification by flash chromatography (eluting with ethyl acetate/hexane, 3:2) afforded the 3-ethyl-3-hydroxy-1-(4-methanesulfonyl-phenyl)-pentan-2-one compound as a white foam.

PREPARATION OF SULFONES

Sulfone 01

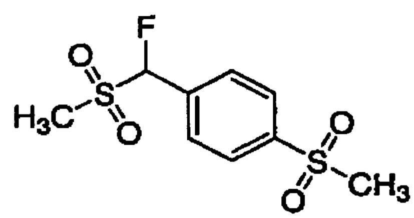
1-Methanesulfonyl-4-methanesulfonylmethyl-benzene



To a solution of 4-methanesulfonylbenzyl chloride (2g, 10mmol) in DMF (20mL) at 21°C was added sodium methanesulfinate (1.5g, 15mmol). After 18h, the mixture is poured into cold water (100mL), stirred for 30min then filtered off to afford the title compound as a white solid.

Sulfone 02

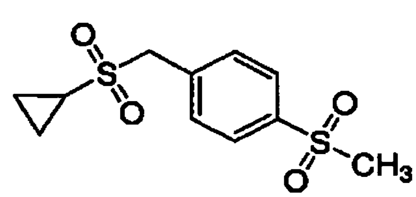
1-(Fluoro-methanesulfonyl-methyl)-4-methanesulfonyl-benzene



To a solution of **Sulfone 01** (275mg, 1.1mmol) in DMF (6mL) at 0°C was added potassium tert-butoxide (1M THF, 1.5mL, 1.5mmol) followed, after 10min, by N-fluorobenzenesulfonimide (419mg, 1.3mmol). The reaction mixture was diluted with a saturated sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with CH_2Cl_2/acetone, 97:3) provided the title compound.

Sulfone 03

1-Cyclopropanesulfonylmethyl-4-methanesulfonyl-benzene



Step 1: (4-Methylsulfanyl-phenyl)-methanethiol disulfide

A solution of sulfur (1g, 29mmol) in benzene (60mL), PEG 400 (1 drop) and NaOH (5N, 46mL, 232mmol) was heated at 65°C for 3h. 4-methylthiobenzyl chloride (4g, 23mmol) and a catalytic amount of tetrabutylammonium iodide was added and the mixture stirred at 65°C for 2h. The reaction was cooled at 21°C and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. The residue was stirred vigorously in ethanol/ether for 1h then filtered to afford the (4-methylsulfanyl-phenyl)-methanethiol disulfide compound as a pale rose powder.

Step 2: 1-Cyclopropylsulfanylmethyl-4-methylsulfanyl-benzene

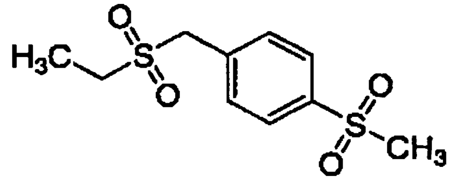
To a solution of (4-methylsulfanyl-phenyl)-methanethiol disulfide from **Step 1** in THF (50mL) at 21°C was added cyclopropylmagnesium bromide (excess) dropwise. The reaction mixture was stirred 18h at 21°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 98:2) provided the 1-cyclopropylsulfanylmethyl-4-methylsulfanyl-benzene compound as an oil.

Step 3: 1-Cyclopropanesulfonylmethyl-4-methanesulfonyl-benzene

Following the procedures described in **Example 16**, but substituting 1-cyclopropylsulfanylmethyl-4-methylsulfanyl-benzene thioether from **Step 2** for **Example 15** and purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50 to 0:100) provided the 1-cyclopropanesulfonylmethyl-4-methanesulfonyl-benzene compound as a solid.

Sulfone 04

1-Ethanesulfonylmethyl-4-methanesulfonyl-benzene



Step 1: 1-Ethylsulfanylmethyl-4-methanesulfonyl-benzene

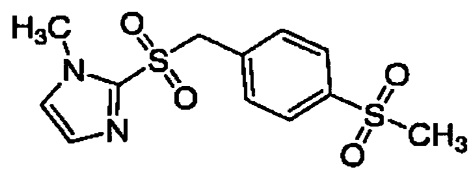
To a solution of ethanethiol (0.3mL, 4.9mmol) and 4-methanesulfonylbenzyl chloride (1g, 4,9mmol) in DMF (10mL) at 21°C was added cesium carbonate (0.8g, 2.5mmol). After 18h, the reaction mixture was poured into water and then filtered off to provide the 1-ethylsulfanylmethyl-4-methanesulfonyl-benzene compound as a white solid.

Step 2: 1-Ethanesulfonylmethyl-4-methanesulfonyl-benzene

Following the procedures described in Example 16, but substituting the 1-ethylsulfanylmethyl-4-methanesulfonyl-benzene thioether from **Step 1 for Example 15**, the 1-ethanesulfonylmethyl-4-methanesulfonyl-benzene compound was isolated as a white solid.

Sulfone 05

2-(4-Methanesulfonyl-phenylmethanesulfonyl)-1-methyl-1H-imidazole



Step 1: 2-(4-Methanesulfonyl-benzylsulfanyl)-1-methyl-1H-imidazole

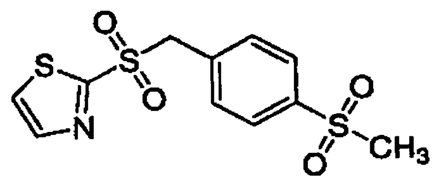
To a solution of 2-mercapto-N-methylimidazole (570mg, 4.9mmol) and 4-methanesulfonylbenzyl chloride (1g, 4,9mmol) in DMF (10mL) at 21°C was added cesium carbonate (0.8g, 2.5mmol). After 18h, the reaction mixture was diluted with water and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated to provide the 2-(4-methanesulfonyl-benzylsulfanyl)-1-methyl-1H-imidazole compound as a white solid.

Step 2: 2-(4-Methanesulfonyl-phenylmethanesulfonyl)-1-methyl-1H-imidazole

Following the procedures described in **Example 16**, but substituting the 2-(4-methanesulfonyl-benzylsulfanyl)-1-methyl-1H-imidazole thioether from **Step 1** for **Example 15**, the 2-(4-methanesulfonyl-phenylmethanesulfonyl)-1-methyl-1H-imidazole compound was isolated as a white solid.

Sulfone 06

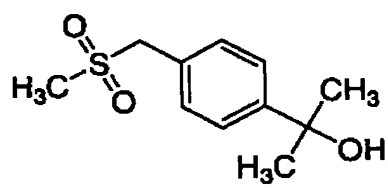
2-(4-Methanesulfonyl-phenylmethanesulfonyl)-thiazole



Following the procedures described in **Sulfone 04**, but substituting 2-mercaptothiazole for ethanethiol, the title compound was obtained as a white solid.

Sulfone 07

2-(4-Methanesulfonylmethyl-phenyl)-propan-2-ol



Step 1: 4-Methanesulfonylmethyl-benzoic acid methyl ester

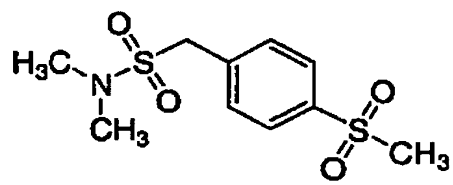
Following the procedures described in **Sulfone 01**, but substituting 4-carboxymethylbenzyl chloride for 4-methanesulfonylbenzyl chloride, the 4-methanesulfonylmethyl-benzoic acid methyl ester compound was obtained as a white solid.

Step 2: 2-(4-Methanesulfonylmethyl-phenyl)-propan-2-ol

Following the procedures described in **Example 29**, but substituting the 4-methanesulfonylmethyl-benzoic acid methyl ester from **Step 1 for Example 27**, the 2-(4-methanesulfonylmethyl-phenyl)-propan-2-ol compound was obtained as a white solid.

Sulfone 08

C-(4-Methanesulfonyl-phenyl)-N,N-dimethyl-methanesulfonamide



Step 1: (4-Methanesulfonyl-phenyl)-methanethiol

To a solution of potassium acetate (5.86g, 51mmol) in THF/DMF (3:1, 400mL) was added 4-methanesulfonylbenzyl chloride (10g, 49mmol). After 3h at 21°C, the resulting reaction mixture was quenched with LiOH (1M) and stirred again for 2h. The mixture was diluted with HCl 10% solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with CH_2Cl_2) provided the (4-methanesulfonyl-phenyl)-methanethiol compound.

Step 2: (4-Methanesulfonyl-phenyl)-methanesulfonyl chloride

To a solution of the (4-methanesulfonyl-phenyl)-methanethiol from **Step 1** (7.3g, 36mmol) in AcOH (75mL) was added water (25mL). Then, chlorine was bubbled in the resulting mixture for 2min. The mixture was diluted with water and filtered to provide the (4-methanesulfonyl-phenyl)-methanesulfonyl chloride.

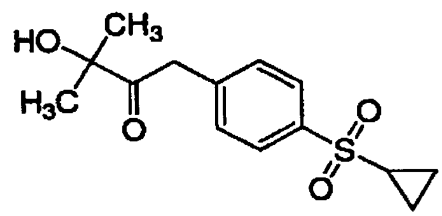
Step 3: C-(4-Methanesulfonyl-phenyl)-N,N-dimethyl-methanesulfonamide

To a solution of (4-methanesulfonyl-phenyl)-methanesulfonyl chloride from **Step 2** (1.0g, 3.7mmol) in CH_2Cl_2 (40mL) was added dimethylamine (0.42g, 9.3mmol) dropwise. After 18h, the resulting reaction mixture was diluted with a

saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (HCl 10%, $NaHCO_3$, brine), dried ($MgSO_4$), filtered, and concentrated to provided the C-(4-methanesulfonyl-phenyl)-N,N-dimethyl-methanesulfonamide compound.

Sulfone 09

1-(4-Cyclopropanesulfonyl-phenyl)-3-hydroxy-3-methyl-butan-2-one



Step 1: 4-bromobenzene disulfide

To a solution of 4-bromothiophenol (16g, 85mmol) in CH_2Cl_2 (85mL) was added iodine (10.7g, 42mmol, in CH_2Cl_2) and triethylamine (11.8mL, 85mmol). After 3h the resulting reaction mixture was diluted with a sodium bisulfite solution and ethyl acetate. The organic extracts were washed (1N NaOH, brine), dried ($MgSO_4$), filtered and concentrated. The resulting residue was stirred vigorously in hexane/ether for 1h then filtered to afford the 4-bromobenzene disulfide compound as a white powder.

Step 2: 1-Bromo-4-cyclopropylsulfanyl-benzene

Following the procedures described in **Sulfone 03, Step 2** and purification by flash chromatography (eluting with hexane) provided the 1-bromo-4-cyclopropylsulfanyl-benzene compound.

Step 3: 1-(4-Cyclopropylsulfanyl-phenyl)-3-hydroxy-3-methyl-butan-2-one

Following the procedures described in **Ketone 01**, but substituting the 1-bromo-4-cyclopropylsulfanyl-benzene from **Step 2** for 4-bromothioanisole, the 1-

(4-cyclopropylsulfanyl-phenyl)-3-hydroxy-3-methyl-butan-2-one compound was obtained.

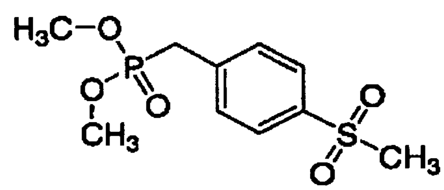
Step 4: 1-(4-Cyclopropanesulfonyl-phenyl)-3-hydroxy-3-methyl-butan-2-one

Following the procedures described in **Ketone 02**, but substituting the 1-(4-cyclopropylsulfanyl-phenyl)-3-hydroxy-3-methyl-butan-2-one from **Step 3** for **Ketone 01**, the 1-(4-cyclopropanesulfonyl-phenyl)-3-hydroxy-3-methyl-butan-2-one compound was obtained.

PREPARATION OF PHOSPHONATES

Phosphonate 01

(4-Methanesulfonyl-benzyl)-phosphonic acid dimethyl ester



Step 1: (4-Methylsulfanyl-benzyl)-phosphonic acid dimethyl ester

To trimethylphosphite (8.6g, 70mmol) at 140°C was added 4-methylthiobenzyl chloride (10g, 58mmol). The resulting mixture was stirred at 140°C for 18h, cooled at 21°C then diluted with HCl 10% and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (eluting with ethyl acetate) provided the (4-methylsulfanyl-benzyl)-phosphonic acid dimethyl ester compound.

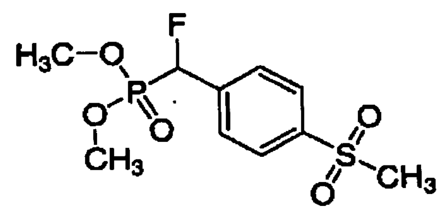
Step 2: (4-Methanesulfonyl-benzyl)-phosphonic acid dimethyl ester

Following the procedures described in **Example 16**, but substituting (4-methylsulfanyl-benzyl)-phosphonic acid dimethyl ester from **Step 1** for **Example**

15, the (4-methanesulfonyl-benzyl)-phosphonic acid dimethyl ester compound was isolated.

Phosphonate 02

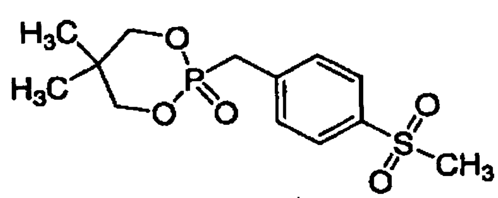
[Fluoro-(4-methanesulfonyl-phenyl)-methyl]-phosphonic acid dimethyl ester



Following the procedures described in **Example 37**, but substituting **Phosphonate 01** for **Example 1**, using THF as solvent, and purification by flash chromatography (eluting with toluene/acetone, 1:1) afforded the title compound.

Phosphonate 03

2-(4-Methanesulfonyl-benzyl)-5,5-dimethyl-[1,3,2]dioxaphosphinane 2-oxide



Step 1: (4-Methanesulfonyl-benzyl)-phosphonic acid

To a solution of **Phosphonate 01** (5.74g, 20.6mmol) in $CHCl_3$ (50mL) was added TMSBr (27mL, 206mmol) dropwise. The resulting reaction mixture was stirred 18h at 21°C, concentrated under vacuum, and diluted with $CHCl_3$ and EtOH. After 2h of stirring at 21°C, the mixture was concentrated again under vacuum. The resulting residue was crystallized from CH_2Cl_2/hexane as a white solid.

Step 2: (4-Methanesulfonyl-benzyl)-phosphonoyl chloride

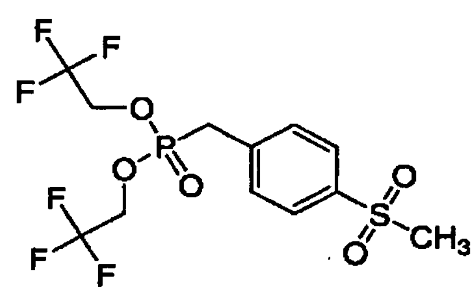
To a solution of (4-methanesulfonyl-benzyl)-phosphonic acid from **Step 1** (5.3g, 21mmol) in CH_2Cl_2 (200mL) was added oxalyl chloride (4mL, 45mmol) dropwise and a few drops of DMF. After 5 days at 21°C, the solvent was evaporated and the residue was used as such in the next step.

Step 3: 2-(4-Methanesulfonyl-benzyl)-5,5-dimethyl-[1,3,2]dioxaphosphinane 2-oxide

To a solution of (4-Methanesulfonyl-benzyl)-phosphonoyl chloride from **Step 2** (100mg, 0.35mmol) in CH_2Cl_2 (5mL) was added triethylamine (0.1mL, 0.7mmol) and 2,2-dimethyl-1,3-propanediol (48mg, 0.47mmol). The resulting reaction mixture was stirred 48h at 21°C, then diluted with water and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by crystallization from CH_2Cl_2/hexane provided the 2-(4-methanesulfonyl-benzyl)-5,5-dimethyl-[1,3,2]dioxaphosphinane 2-oxide compound as a white solid.

Phosphonate 04

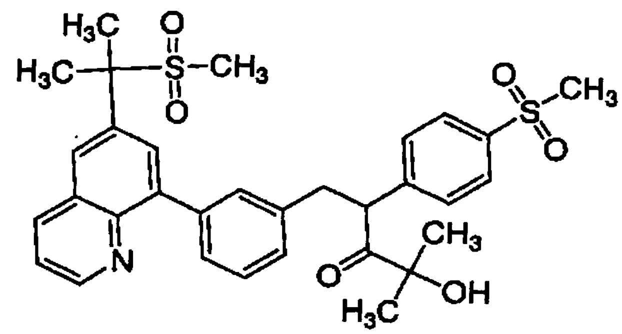
(4-Methanesulfonyl-benzyl)-phosphonic acid bis-(2,2,2-trifluoro-ethyl) ester



Following the procedures described in **Phosphonate 03**, but substituting 2,2,2-trifluoroethanol for 2,2-dimethyl-1,3-propanediol, the title compound was obtained.

EXAMPLE 1

4-Hydroxy-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-4-methyl-pentan-3-one

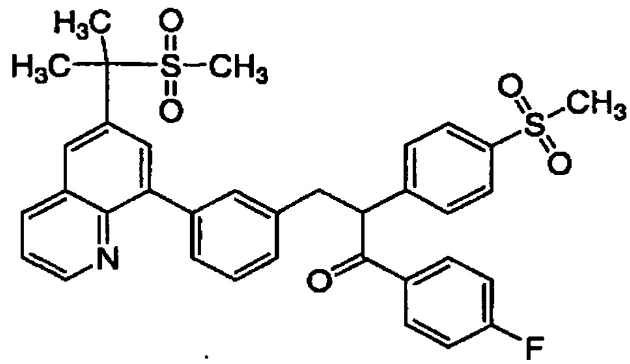


To a solution of **Ketone 02** in THF/DMF (4:1, 0.08M) at 0°C was added potassium tert-butoxide (1M, THF,1.0 eq) dropwise followed after 10 min by **Quinoline 01** (1.0 eq) dissolved in DMF (2M). The resulting reaction mixture was stirred at 21°C for 3h and diluted with a saturated ammonium acetate solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (eluting with ethyl acetate/dichloromethane, 60:40) provided the title compound as a white foam. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH, 65:35, retention time 12.26 and 13.36 min) to give **Example 1A** (first to elute, $[\alpha]_D$ 77.3 c = 0.94 CH_2Cl_2) and **Example 1B.**

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 1H), 8.45 (dd, 1H), 8.26 (d, 1H), 8.05 (d, 1H), 7.86 (d, 2H), 7.68 (d, 2H), 7.57 (m, 2H), 7.50 (d, 1H), 7.35 (t, 1H), 7.21 (d, 1H), 5.18 (dd, 1H), 4.46 (s, OH), 3.45 (dd, 1H), 3.08 (dd, 1H), 3.05 (s, 3H), 2.7 (s, 3H), 1.98 (s, 6H), 1.1 (s, 3H), 1.05 (s, 3H).

EXAMPLE 2

1-(4-Fluoro-phenyl)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one

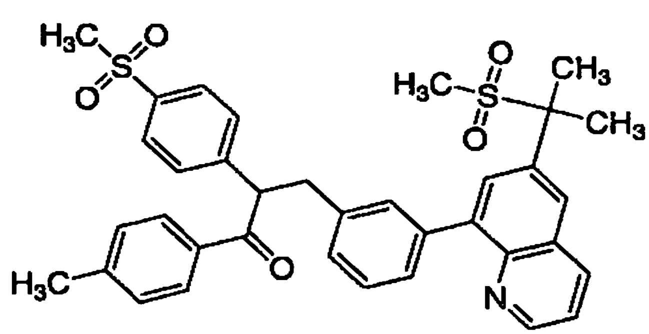


Following the procedures described in **Example 1**, but substituting **Ketone 03** for **Ketone 02**, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, acetone-d_6): δ 8.88 (dd, 1H), 8.68 (dd, 1H), 8.43 (dd, 1H), 8.25 (d, 1H), 8.19-8.15 (m, 2H), 8.03 (d, 1H), 7.86 (d, 2H), 7.71 (d, 2H), 7.64 (s, 1H), 7.55 (dd, 1H), 7.50 (app d, 1H), 7.30 (t, 1H), 7.24 (app d, 1H), 7.19 (t, 2H), 5.47 (t, 1H), 3.22 (dd, 1H), 3.01 (s, 3H), 2.71 (s, 3H), 1.97 (s, 6H).

EXAMPLE 3

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-p-tolyl-propan-1-one

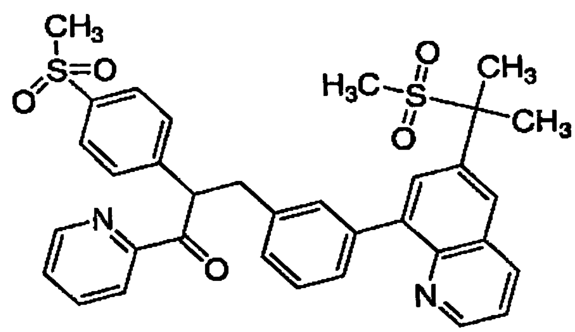


Following the procedures described in **Example 1**, but substituting **Ketone 04** for **Ketone 02**, the title compound was obtained.

^{1}H NMR (400MHz, acetone-d_6): δ 8.88 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.02 (d, 1H), 7.98 (d, 2H), 7.85 (d, 2H), 7.71 (d, 2H), 7.64 (s, 1H), 7.55 (dd, 1H), 7.50 (app d, 1H), 7.30 (t, 1H), 7.25 (app d, 3H), 5.45 (t, 1H), 3.68 (dd, 1H), 3.20 (dd, 1H), 3.01 (s, 3H), 2.70 (s, 3H), 2.32 (s, 3H), 1.97 (s, 6H).

EXAMPLE 4

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-pyridin-2-yl-propan-1-one

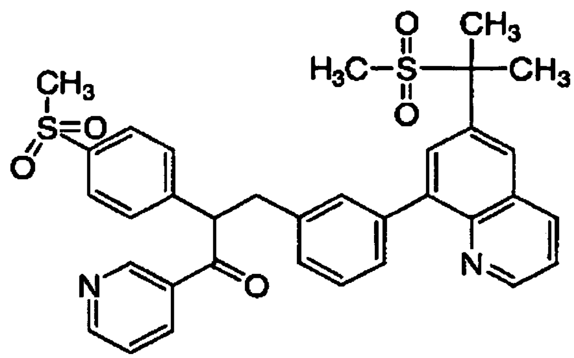


Following the procedures described in **Example 1**, but substituting **Ketone 05** for **Ketone 02**, the title compound was obtained.

^{1}H NMR (400MHz, acetone-d_6): δ 8.86 (dd, 1H), 8.69 (d, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.02-8.01 (m, 2H), 7.94 (td, 1H), 7.83 (d, 2H), 7.72 (d, 2H), 7.64 (s, 1H), 7.59-7.56 (m, 1H), 7.54 (dd, 1H), 7.50 (app d, 1H), 7.33-7.26 (m, 2H), 6.06 (t, 1H), 3.70 (dd, 1H), 3.27 (dd, 1H), 3.01 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 5

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-pyridin-3-yl-propan-1-one

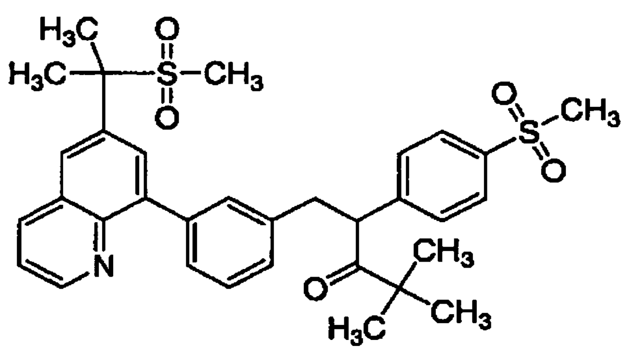


Following the procedures described in **Example 1**, but substituting **Ketone 06** for **Ketone 02**, the title compound was obtained.

[1]H NMR (400MHz, acetone-d_6): δ 9.22 (d, 1H), 8.89 (dd, 1H), 8.69 (dd, 1H), 8.43 (dd, 1H), 8.36 (dt, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.87 (d, 2H), 7.73 (d, 2H), 7.65 (s, 1H), 7.55 (dd, 1H), 7.49 (app d, 1H), 7.45 (dd, 1H), 7.31 (t, 1H), 7.25 (app d, 1H), 5.52 (t, 1H), 3.70 (dd, 1H), 3.25 (dd, 1H), 3.01 (s, 3H), 2.71 (s, 3H), 1.97 (s, 6H).

EXAMPLE 6

1-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-4,4-dimethyl-pentan-3-one

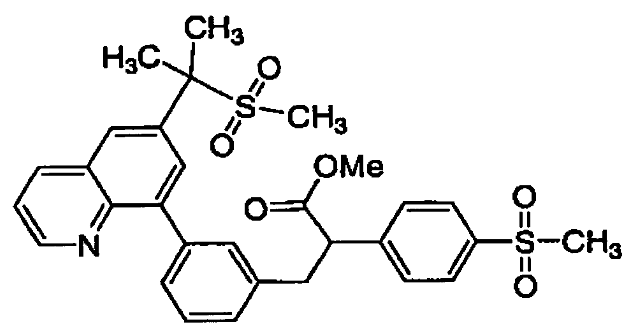


Following the procedures described in **Example 1**, but substituting **Ketone 07** for **Ketone 02**, the title compound was obtained as white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.87 (dd, 2H), 7.56 (m, 2H), 7.50 (d, 1H), 7.33 (t, 1H), 7.21 (d, 1H), 7.2 (dd, 2H), 4.89 (dd, 1H), 3.39 (dd, 1H), 3.06 (s, 3H), 3.04 (dd, 1H), 2.71 (s, 3H), 1.98 (s, 6H), 0.95 (s, 9H). **99254-47**

EXAMPLE 7

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester

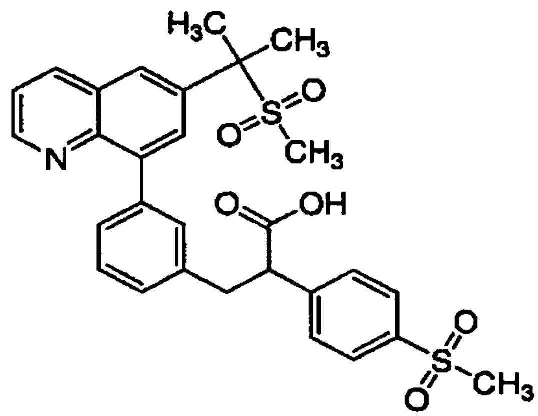


To a solution of **Ester 01** (1.26g, 5.5mmol) in THF (80mL) at -78°C was added LiHMDS (1M, THF, 6.6mL, 6.6mmol) dropwise followed, after 30min, **Quinoline 01** (2.1g, 5.0mmol) dissolved in DMF (8mL). The reaction mixture was stirred at -78°C for 2h and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 40:60) provided the title compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.92 (dd, 1H), 8.43 (dd, 1H), 8.25 (d, 1H), 8.06 (d, 1H), 7.99 (d, 2H), 7.9 (d, 2H), 7.57 (m, 3H), 7.34 (t, 1H), 7.24 (d, 1H), 4.24 (t, 1H), 3.62 (s, 3H), 3.54 (dd, 1H), 3.29 (dd, 1H), 3.07 (s, 3H), 1.99 (s, 6H).

EXAMPLE 8

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid

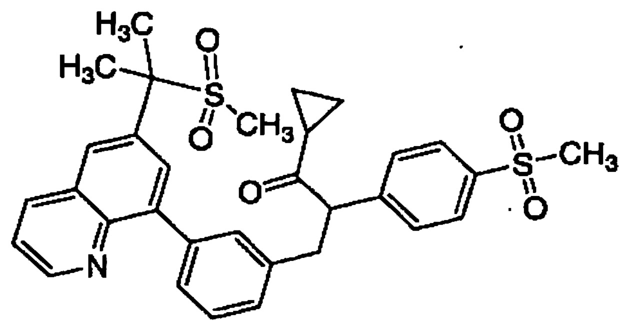


To a solution of **Example 7** (130mg, 0.23mmol) in THF/MeOH/H_2O (2:2:1, 5mL) was added LiOH (2M, 0.35mL, 0.69mmol). The resulting mixture was stirred at 21°C 18h, acidified with HCl 10% and diluted with ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. The title compound was obtained as a white powder after sonication in ether/hexane and filtration.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.92 (dd, 1H), 8.43 (dd, 1H), 8.25 (d, 1H), 8.06 (d, 1H), 7.9 (d, 2H), 7.70 (d, 2H), 7.62 (s, 1H), 7.54 (m, 2H), 7.34 (t, 1H), 7.26 (d, 1H), 4.22 (dd, 1H), 3.55 (dd, 1H), 3.39 (dd, 1H), 3.07 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H).

EXAMPLE 9

1-Cyclopropyl-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one



Step 1: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-N-methoxy-N-methyl-propionamide

To a solution of N,O-dimethylhydroxylamine (free base, 260mg, 4.2mmol) in THF at -78°C was added MeMgBr (3M, ether, 1.4mL, 4.2mmol) dropwise (internal temperature < -65°C) followed, after 30 min, by **Example 7** (600mg, 1.06mmol, in THF). The resulting mixture was warmed slowly to 21°C, diluted with ethyl acetate and saturated ammonium chloride solution. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:4 to 1:9) provided the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-N-methoxy-N-methyl-propionamide compound as a white foam.

Step 2: 1-Cyclopropyl-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one

Anhydrous $CeCl_3$ (266mg, 1.26mmol) was heated 2h at 130°C under high vacuum, refluxed in THF (10mL) for 1h then cooled to 0°C. To the resulting white suspension at 0°C was added freshly prepared cyclopropylmagnesium bromide (0.6M, THF, 2.1mL, 1.25mmol) and the resulting mixture stirred at 0°C for 1h then cooled to -78°C. The 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-N-methoxy-N-methyl-propionamide from **Step 1** (in THF, 150 mg, 0.25mmol) was added and the mixture warmed to 0°C for

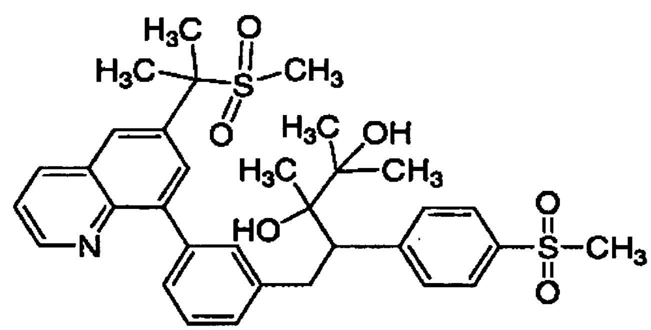
1h, diluted with ethyl acetate and saturated ammonium chloride solution. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:4) provided the 1-cyclopropyl-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 6H), 8.42 (dd, 1H), 8.25 (d, 1H), 8.06 (d, 1H), 7.95 (d, 2H), 7.63 (d, 2H), 7.54 (m, 3H), 7.31 (t, 1H), 7.20 (d, 1H), 4.61 (t, 1H), 3.56 (dd, 1H), 3.09 (dd, 1H), 3.05 (s, 3H), 2.71 (s, 3H), 2.06 (m, 1H), 1.98 (s, 6H), 0.9-0.7 (m, 4H).

An alternate synthesis of **Example 9** is by following the procedures described above in **Example 1,** but substituting **Ketone 08** for **Ketone 02.**

EXAMPLE 10

5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-(4-methanesulfonyl-phenyl)-2,3-dimethyl-pentane-2,3-diol



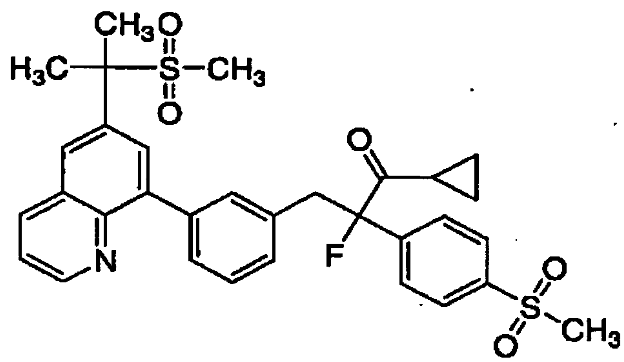
Using **Example 01** as the starting material and following the procedures described above in **Example 9, Step 2,** and substituting methylmagnesium bromide for cyclopropyl magnesium bromide, the title compound was obtained as a white solid (one pair of enantiomer).

^{1}H NMR (400MHz, acetone-*d6*): δ 8.89 (dd, 1H), 8.38 (dd, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.71 (d, 2H), 7.61 (d, 2H), 7.50 (dd, 1H), 7.47 (s, 1H), 7.39 (d,

1H), 7.16 (t, 1H), 7.08 (d, 1H), 3.74 (m, 2H), 3.63 (s, 1H), 3.29 (s, 1H), 3.19 (m, 1H), 2.93 (s, 3H), 2.70 (s, 3H), 1.95 (s, 6H), 1.41 (s, 6H), 1.32 (s, 3H).

EXAMPLE 11

1-Cyclopropyl-2-fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one

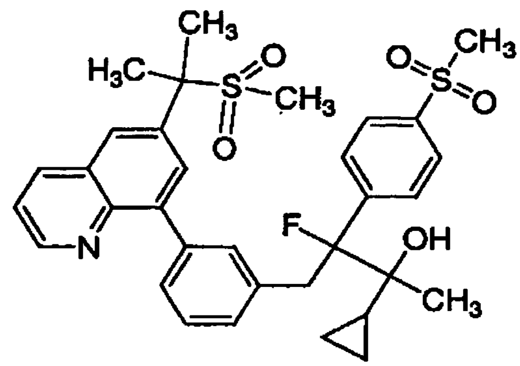


To a solution of **Example 9** (1.5g, 2.62mmol) in THF/DMF (3:1, 13mL) at -78°C was added potassium tert-butoxide (1M THF, 2.9mL, 2.9mmol), followed by N-fluorobenzenesulfonimide (1.63g, 5.2mmol). The resulting reaction mixture was stirred 2h at -78°C, then quenched with AcOH (2 drops) and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 80:20) provided the title compound.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.40 (dd, 1H), 8.24 (d, 1H), 8.05 (d, 1H), 7.97 (d, 2H), 7.71 (d, 2H), 7.59 (d, 1H), 7.55 (s, 1H), 7.53 (dd, 1H), 7.34 (t, 1H), 7.14 (d, 1H), 3.78 (dd, 1H), 3.52 (dd, 1H), 3.09 (s, 3H), 2.70 (s, 3H), 2.49-2.41 (m, 1H), 1.98 (s, 6H), 0.91-0.85 (m, 4H).

EXAMPLE 12

2-Cyclopropyl-3-fluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol



Using **Example 11** as starting material and following the procedures described below in **Example 29,** the title compound was obtained as a white solid (9:1 mixture of diastereoisomers). The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH, 1;1, retention time 21 and 29 min) to give **Example 12A** and **Example 12B.**

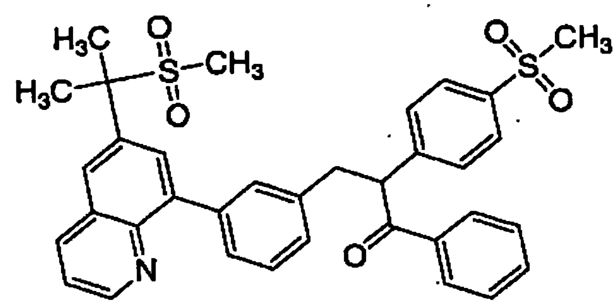
^{1}H NMR (400MHz, acetone-*d6*): (major isomer) δ 8.88 (dd, 1H), 8.38 (dd, 1H), 8.20 (d, 1H), 7.91 (d, 1H), 7.83 (d, 2H), 7.78 (d, 2H), 7.51 (dd, 1H), 7.45 (s, 1H), 7.44 (d, 1H), 7.18 (t, 1H), 7.14 (d, 1H), 4.11 (s, OH), 3.83 (s, 1H), 3.77 (dd, 1H), 2.97 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.34 (d, 3H), 0.96-0.92 (m, 1H), 0.34-0.22 (m, 3H), 0.14-0.10 (m, 1H). LRMS (CI) 610 $(M+H)^+$.

The other pair of enantiomers can be obtained using **Example 14** as the starting material and following procedures described in **Example 11** followed with the procedures described above in **Example 9, Step 2** (85:15 mixture of diastereoisomers).

^{1}H NMR (400MHz, acetone-*d6*): δ 8.88 (dd, 1H), 8.40 (dd, 1H), 8.21 (d, 1H), 7.91 (d, 1H), 7.79 (m, 4H), 7.52 (dd, 1H), 7.43 (m, 2H), 7.15 (m, 2H), 4.1-3.6 (m, 3H), 3.89 (s, 3H), 2.70 (s, 3H), 1.97 (d, 6H), 1.29 (m, 1H), 1.09 (d, 3H), 0.81 (m, 1H), 0.56 (m, 1H), 0.38 (m, 2H).

EXAMPLE 13

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-phenyl-propan-1-one



Step 1: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester

To a solution of **Ester 04** (4.0g, 20mmol) in THF (50mL) at -78°C was added KHMDS (0.5M, Tol, 41mL, 20.5mmol) dropwise. The resulting reaction mixture was stirred 0.5h at -78°C then cannulated into **Quinoline 02** (2.95g, 6.8mmol) in THF (50mL) at 21°C. After 15min, the mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester compound as a white foam.

Step 2: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionaldehyde

To a solution of 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester from **Step 1** (1.48g, 7.5mmol) in CH_2Cl_2 (80mL) at -78°C was added dibal-H (1.6mL, 7.8mmol). The resulting reaction mixture was stirred 1h at -78°C, then quenched with sodium potassium tartrate solution and stirred at 21°C for 3h. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated to provided the 3-{3-

[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionaldehyde compound as a white foam.

Step 3: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-1-phenyl-propan-1-ol

To a solution of 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionaldehyde from **Step 2** (150mg, 0.3mmol) in CH_2Cl_2 (6mL) at 21°C was added phenylmagnesium chloride (2M, THF, 0.45mL, 0.9mmol) dropwise. The resulting reaction mixture was stirred 0.5h at 21°C then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. The crude oil was used as such in the next step.

Step 4: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-1-phenyl-propan-1-one

To a solution of the crude oil from **Step 3** in CH_2Cl_2 (5mL) at 21°C was added Dess-Martin periodinane (255mg, 0.6mmol) portionwise. The resulting reaction mixture was stirred 2h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-1-phenyl-propan-1-one compound as a white foam.

Step 5: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-phenyl-propan-1-one

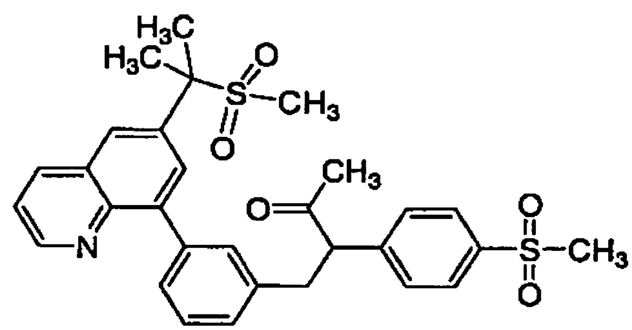
To a solution of 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-1-phenyl-propan-1-one from **Step 4** (55mg, 0.095mmol) in THF/MeOH/H_2O (2:1:1, 5mL) at 21°C was added OXONE® (0.1g, 0.16mmol). The resulting reaction mixture was stirred 2h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were

washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. The residue was stirred vigorously in hexane/ether for 1h then filtered to afford the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-phenyl-propan-1-one compound as a white powder.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.87 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.08 (d, 2H), 8.03 (d, 1H), 7.85 (d, 2H), 7.71 (d, 2H), 7.65 (s, 1H), 7.56-7.42 (m, 5H), 7.28 (m, 2H), 5.5 (t, 1H), 3.69 (dd, 1H), 3.23 (dd, 1H), 3.00 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H). **99020-173**

EXAMPLE 14

4-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-one

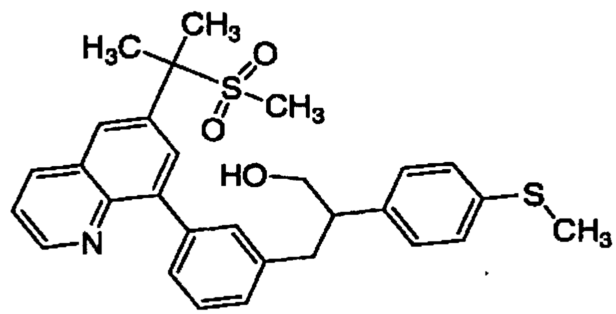


Following the procedures described above in **Example 13**, but substituting methylmagnesiumbromide for phenylmagnesium bromide in **Step 3**, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.92 (dd, 1H), 8.43 (dd, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.95 (d, 2H), 7.62 (d, 2H), 7.60-7.52 (m, 3H), 7.31 (t, 1H), 7.18 (d, 1H), 4.50 (t, 1H), 3.52 (dd, 1H), 3.10 (dd, 1H), 3.05 (s, 3H), 2.83 (s, 3H), 2.11 (s, 3H), 1.98 (s, 6H).

EXAMPLE 15

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propan-1-ol

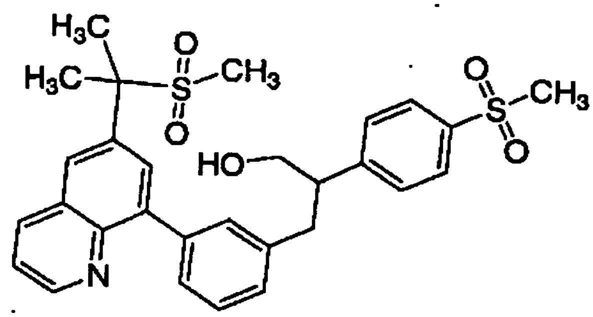


To a solution of the ester from **Step 1, Example 13** (1.0g, 5mmol) in CH_2Cl_2 (25mL) at -78°C was added dibal-H (2.1mL, 12mmol). The resulting reaction mixture was warmed slowly to 21°C, then quenched with sodium potassium tartrate solution and stirred at 21°C for 3h. The reaction mixture was diluted with ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the title compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.91 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.01 (d, 1H), 7.56 (dd, 1H), 7.51 (m, 2H), 7.29 (t, 1H), 7.24-7.14 (m, 6H), 3.75 (d, 2H), 3.27 (dd, 1H), 3.14 (m, 1H), 2.96 (dd, 1H), 2.70 (s, 3H), 2.42 (s, 3H), 1.98 (s, 6H).

EXAMPLE 16

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol

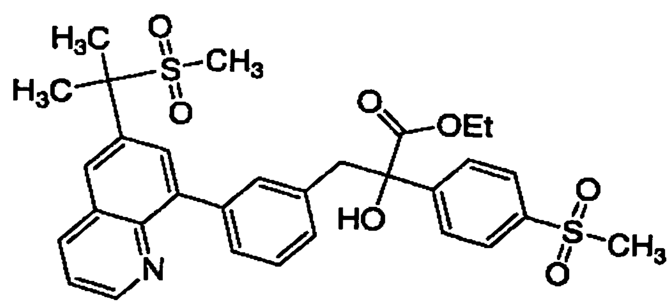


To a solution of **Example 15** (350mg, 0.69mmol) in THF/MeOH/H_2O (2:1:1, 15mL) at 21°C was added OXONE® (1.1g, 1.8mmol). The resulting reaction mixture was stirred 2h at 21°C then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated to afford the title compound as a pale yellow foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.04 (d, 1H), 7.82 (d, 2H), 7.55 (m, 5H), 7.31 (t, 1H), 7.20 (d, 1H), 3.83 (d, 2H), 3.34 (m, 2H), 3.05 (m, 1H), 3.03 (s, 3H), 2.70 (s, 3H), 1.98 (s, 6H).

EXAMPLE 17

2-Hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester



Step 1: 2-Hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid ethyl ester

To a solution of **Ester 02** (220mg, 0.97mmol) in THF (6mL) at -78°C was added potassium tert-butoxide (1M, THF, 2.1mL,2.1mmol) dropwise. The resulting reaction mixture was warmed to -40°C for 20 min, then **Quinoline 01** (0.25M, THF, 3mL) was added. The reaction mixture was warmed from -40°C to -20°C over a 2h period, then quenched with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the 2-hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid ethyl ester compound as a white foam.

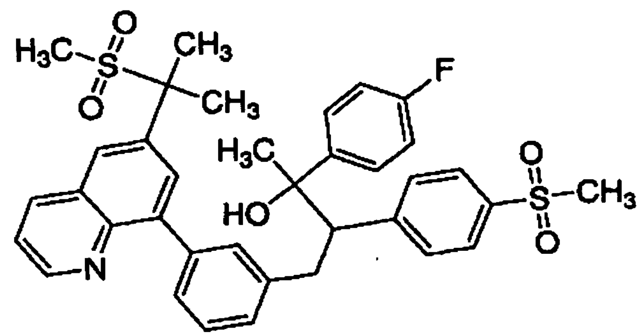
Step 2: 2-Hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester

Using the 2-hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid ethyl ester from **Step 1** and following the procedures described in **Example 16**, and purification by flash chromatography (eluting with hexane/ethyl acetate, 1:4) provided the 2-hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.25 (d, 1H), 8.07 (d, 1H), 8.02 (d, 2H), 7.93 (d, 2H), 7.65 (s, 1H), 7.56 (m, 2H), 7.33 (m, 2H), 5.07 (s, OH), 4.17 (m, 2H), 3.71 (d, 1H), 3.33 (d, 1H), 3.07 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H), 1.17 (m, 3H).

EXAMPLE 18

2-(4-Fluoro-phenyl)-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol

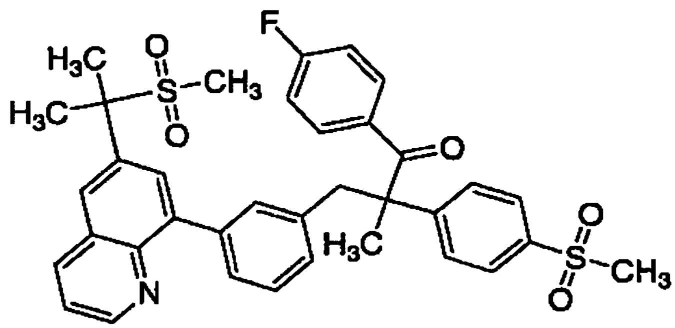


To a solution of **Example 02** (101mg, 0.16mmol) in THF (2mL) at 21°C was added methyl magnesium iodide (3M, Et2O, 0.3mL,0.9mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 18h, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 85:15) provided the title compound as a mixture of diastereoisomers (5:1).

^{1}H NMR (400MHz, acetone-*d6*): δ 8.87 (dd, 1H), 8.38 (dd, 1H), 8.20 (d, 1H), 7.93 (d, 1H), 7.76-7.73 (m, 1H), 7.60 (d, 2H), 7.51 (dd, 1H), 7.41-7.33 (m, 5H), 7.17 (d, 1H), 7.12 (t, 1H), 7.07 (d, 1H), 6.93 (t, 1H), 4.50 (s, OH), 3.62 (dd, 1H), 3.54 (dd, 1H), 3.17 (t, 1H), 2.89 (s, 3H), 2.69 (s, 3H), 1.95 (s, 6H), 1.78 (s, 3H). LRMS (CI) 646 $(M+H)^+$.

EXAMPLE 19

1-(4-Fluoro-phenyl)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-2-methyl-propan-1-one

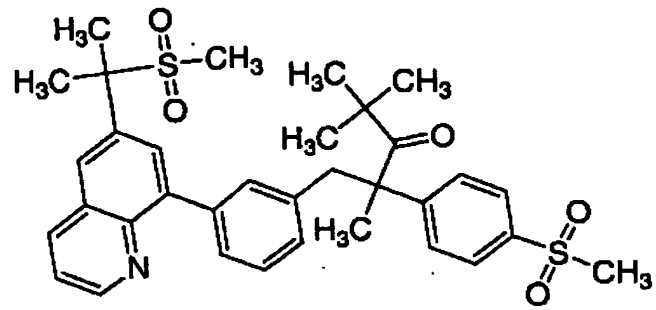


To a solution of **Ketone 09** (171g, 0.56mmol) in THF (3mL) at -20 °C was added potassium tert-butoxide (1M, 0.59mL, 0.59mmol) dropwise followed, after 15min, by **Quinoline 01** (250mg, 0.59mmol) dissolved in DMF (0.4mL). The resulting reaction mixture was stirred at 21°C for 3h and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 85:15) followed by stirring vigorously in hexane/ethyl acetate/ether for 1h then filtered to afford the title compound as a white powder.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.02 (d, 1H), 7.85 (d, 2H), 7.64-7.61 (m, 2H), 7.55 (dd, 1H), 7.50 (d, 3H), 7.21 (d, 1H), 7.18 (s, 1H), 7.08-7.04 (m, 2H), 6.69 (d, 1H), 3.54 (d, 1H), 3.46 (d, 1H), 2.84 (s, 3H), 2.71 (s, 3H), 1.97 (s, 6H), 1.77 (s, 3H). LRMS (CI) 644 $(M+H)^+$.

EXAMPLE 20

1-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-2,4,4-trimethyl-pentan-3-one

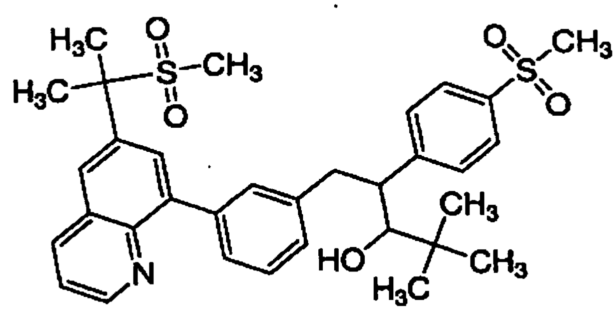


Following the procedures described in **Example 19**, but substituting **Ketone 10** for **Ketone 09** and purification by flash chromatography (eluting with dichloromethane/methanol, 99:1), then stirring vigorously the resulting solid in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.91 (dd, 1H), 8.40 (dd, 1H), 8.22 (d, 1H), 8.01 (d, 1H), 7.83 (d, 2H), 7.53 (dd, 1H), 7.46 (dd, 1H), 7.36 (dd, 2H), 7.14 (t, 1H), 7.09 (s, 1H), 6.55 (s, 1H), 3.28 (d, 1H), 3.18 (d, 1H), 2.81 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.77 (s, 3H), 1.00 (s, 9H). LRMS (CI) 606 $(M+H)^+$.

EXAMPLE 21

1-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-4,4-dimethyl-pentan-3-ol



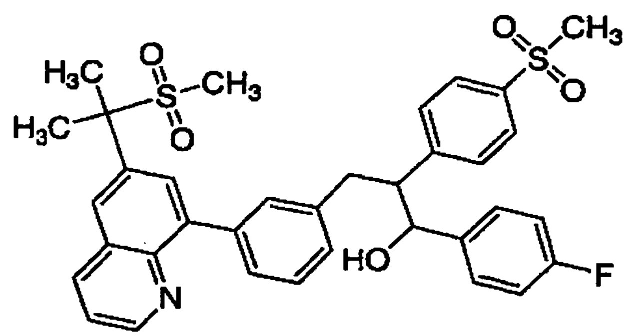
To a solution of **Example 06** (75mg, 0.127mmol) in MeOH (3mL) at -78°C was added sodium borohydride (5mg, 0.13mmol). The resulting reaction mixture was warmed to 21°C then diluted with a saturated ammonium chloride

solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated to provide the title compound as a white foam (one pair of enantiomer).

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 1H), 8.45 (dd, 1H), 8.25 (d, 1H), 8.07 (d, 1H), 7.78 (m, 4H), 7.59 (m, 2H), 7.49 (d, 1H), 7.31 (t, 1H), 7.19 (d, 1H), 4.34 (d, OH), 3.66 (m, 1H), 3.45 (m, 1H), 3.29 (dd, 1H), 3.09 (dd, 1H), 3.0 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H), 0.71 (s, 9H). 99254-62

EXAMPLE 22

1-(4-Fluoro-phenyl)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol

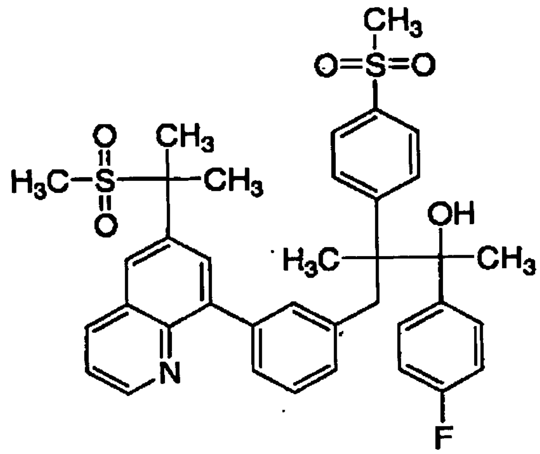


Following the procedures described in **Example 21**, but substituting **Example 02** for **Example 06** and purification by flash chromatography (eluting with dichloromethane/methanol, 99:1), then stirring vigorously the resulting residue in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder (one pair of enantiomer).

^{1}H NMR (400MHz, acetone-d_6): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.03 (d, 1H), 7.72 (d, 2H), 7.56-7.53 (m, 2H); 7.49-7.44 (m, 3H), 7.31-7.23 (m, 3H), 7.18 (d, 1H), 7.00-6.95 (m, 2H), 5.11 (t, 1H), 4.65 (d, OH), 3.53-3.50 (m, 1H), 3.27 (dd, 1H), 3.15 (d, 1H), 2.99 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 23

2-(4-Fluoro-phenyl)-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-3-methyl-butan-2-ol

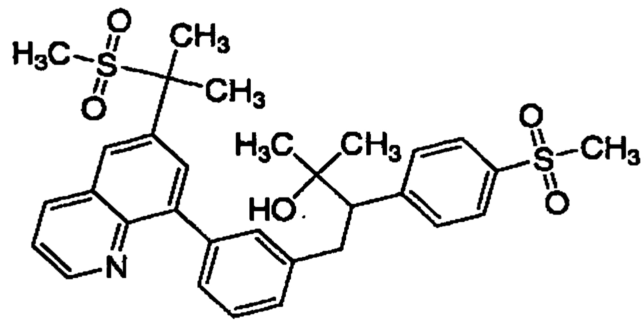


To a solution of **Example 19** (93mg, 0.144mmol) in CH_2Cl_2 (4mL) at -78°C was added methyl magnesium iodide (3M, Et_2O, 0.24mL, 0.8mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 12h, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with dichloromethane/methanol, 99:1, 2 X), then stirring vigorously the resulting residue in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder (mixture of diastereoisomers; 1:1).

^{1}H NMR (400MHz, acetone-*d6*): δ 8.87-8.80 (m, 2H), 8.41-8.35 (m, 2H), 8.19-8.15 (m, 2H), 7.94 (d, 1H), 7.91 (d, 1H), 7.85-7.78 (m, 4H), 7.70-7.66 (d, 2H), 7.61-7.35 (m, 11H), 7.21-7.08 (m, 4H), 7.05-6.98 (m, 3H), 6.86-6.81 (m, 3H), 4.44 (d, 1H), 4.03 (d, 1H), 3.93 (d, 1H), 3.27 (d, 1H), 2.96 (s, 3H), 2.94 (s, 3H), 2.68 (s, 3H), 2.67 (s, 3H), 1.96-1.94 (m, 12H), 1.80 (s, 3H), 1.50 (s, 6H), 1.39 (s, 3H). LRMS (CI) 660 $(M+H)^+$.

EXAMPLE 24

4-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-2-methyl-butan-2-ol

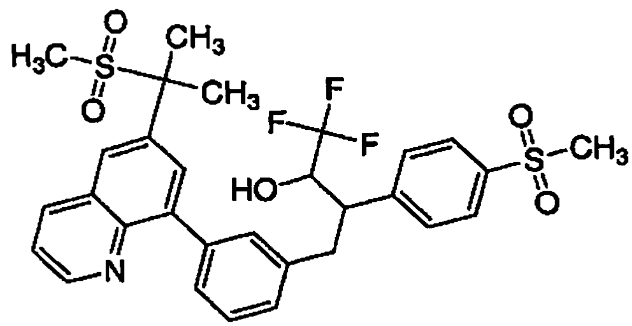


To a solution of **Example 07** (230mg, 0.41mmol) in THF/CH_2Cl_2 (1:1, 6mL) at 21°C was added methyl magnesium bromide (3M, Et_2O, 1.0 mL, 3mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 0.25h, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with ethyl acetate/hexane, 70:30) afforded the title compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.88 (dd, 1H), 8.39 (dd, 1H), 8.21 (d, 1H), 7.94 (d, 1H), 7.77 (d, 2H), 7.61 (d, 2H), 7.52 (dd, 1H), 7.41 (m, 2H), 7.21 (t, 1H), 7.10 (d, 1H), 3.75 (s, OH), 3.52 (m, 3H), 3.26 (m, 1H), 2.98 (s, 3H), 2.70 (s, 3H), 1.96 (s, 6H), 1.5 (s, 3H), 1.17 (s, 3H).

EXAMPLE 25

1,1,1-Trifluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol



Step 1: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionaldehyde

Following the procedures described in **Example 13, Step 2,** but substituting **Example 07** for the ester from **Step 1,** the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionaldehyde compound was isolated as a white foam.

Step 2: 1,1,1-Trifluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol

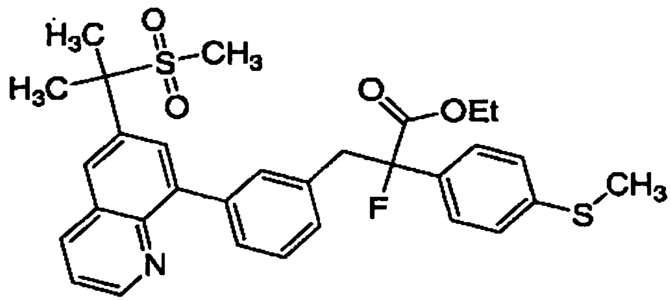
To a solution of 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionaldehyde from **Step 1** (413mg, 0.8mmol) in THF (10mL) at -78°C was added $TMSCF_3$ (0.4mL, 2.7mmol) followed by tetrabutylammonium fluoride (1M, THF, 0.12mL, 120mmol). The resulting reaction mixture was warmed to 0°C, then quenched with tetrabutylammonium fluoride (1M, THF, 1mL, 1mmol). After 1h, the resulting solution was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 60:40 to 10:90) and sonication in hexane/ethyl acetate/ether provided the 1,1,1-trifluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol compound as a white powder (mixture of diastereoisomers).

^{1}H NMR (400MHz, acetone-*d6*, major isomer): δ 8.91 (dd, 1H), 8.43 (dd, 1H), 8.22 (d, 1H), 7.98 (d, 1H), 7.8 (m, 2H), 7.57 (m, 3H), 7.43 (s, 1H), 7.23 (t,

1H), 7.04 (d, 1H), 5.88 (m, OH), 4.5 (m, 1H), 3.6 (m, 2H), 3.2 (m, 1H), 3.04 (s, 3H), 1.97 (s, 6H).

EXAMPLE 26

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid ethyl ester

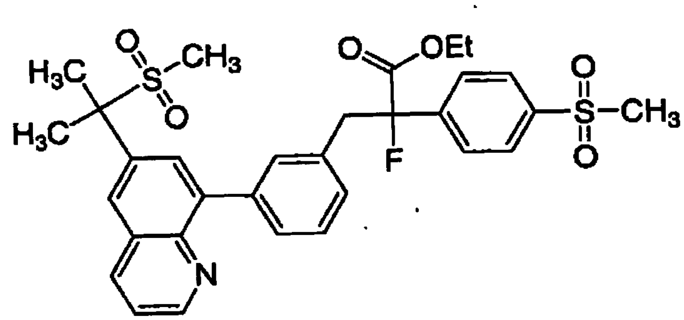


To a solution of **Ester 03** (3.4g, 13mmol) and **Quinoline 01** (4.5g, 11mmol) in THF/DMF (2:1, 60mL) at 0°C was added potassium tert-butoxide (1M, THF, 13.9mL, 13.9mmol) dropwise. After 30min. at 0°C, the resulting reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 9:1) provided the title compound.

^{1}H NMR (400MHz, acetone-d_6): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.05 (d, 1H), 7.63-7.53 (m, 5H), 7.40-7.29 (m, 4H), 4.15 (q, 2H), 3.80 (dd, 1H), 3.53 (dd, 1H), 2.70 (s, 3H), 2.49 (s, 3H), 1.99 (s, 6H), 1.12 (t, 3H).

EXAMPLE 27

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester

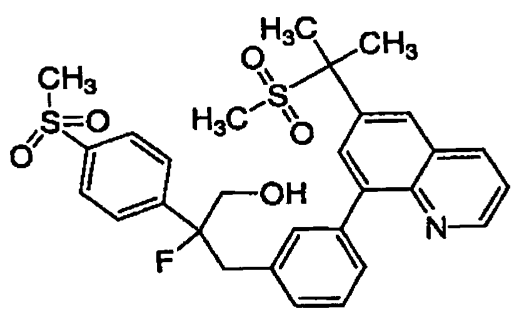


Following the procedures described in **Example 16**, but substituting **Example 26** for **Example 15**, the title compound was obtained.

^{1}H NMR (400MHz, acetone-d_6): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.06 (d, 1H), 8.01 (d, 2H), 7.90 (app d, 2H), 7.64-7.62 (m, 2H), 7.56 (dd, 1H), 7.38 (t, 1H), 7.30 (d, 1H), 4.20 (q, 2H), 3.88 (dd, 1H), 3.60 (dd, 1H), 3.10 (s, 3H), 2.71 (s, 3H), 1.99 (s, 6H), 1.19 (t, 3H).

EXAMPLE 28

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol

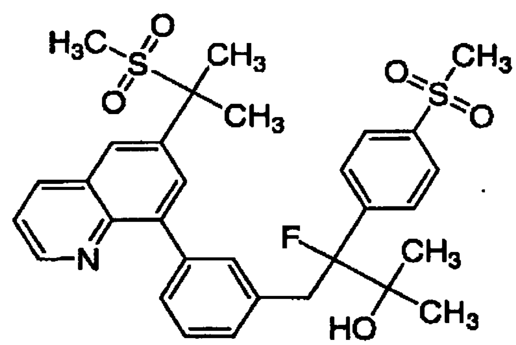


To a solution of **Example 27** (1.15g, 1.95mmol) in CH_2Cl_2 (80mL) at -78°C was added dibal-H (0.82mL, 4.6mmol). The resulting reaction mixture was stirred 1h at -78°C, then quenched with sodium potassium tartrate solution and stirred at 21°C for 3h. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. To the residue dissolved in THF/MeOH (2:1, 22mL) at 21°C was added $NaBH_4$ (180mg, 4.9mmol). After 12h, the reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated to provided the title compound as a white solid.

^{1}H NMR (400MHz, acetone-d_6): δ 8.90 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.02 (d, 1H), 7.89 (d, 2H), 7.68 (d, 2H), 7.60-7.50 (m, 3H), 7.29 (t, 1H), 7.15 (d, 1H), 4.42 (t, OH), 4.03 (dd, 1H), 3.98 (dd, 1H), 3.58 (dd, 1H), 3.44 (dd, 1H), 3.03 (s, 3H), 2.71 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H).

EXAMPLE 29

3-Fluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-2-methyl-butan-2-ol



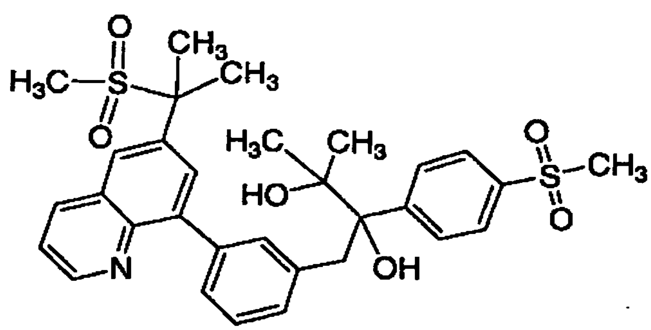
Anhydrous $CeCl_3$ (658mg, 2.67mmol) was heated 1h at 130°C under high vacuum. It was refluxed in THF (8mL) for 1h and then cooled to 0°C. To the resulting white suspension at 0°C, was added methylmagnesium bromide (3M, THF, 0.89mL, 2.7mmol). The resulting mixture was stirred at 0°C for 1h. **Example 27** (267mg, 0.45mmol), dissolved in THF (1mL) was added, and the mixture stirred at

0°C for 0.5h, and diluted with ethyl acetate and saturated ammonium chloride solution. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 9:1) and stirring vigorously in ethyl acetate/ether for 1h, then filtering afforded the title compound as a white powder. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH, 50:50, retention time 6.82 and 9.27 min) to give **Example 29A** and **Example 29B**.

^{1}H NMR (400MHz, acetone-d_6): δ 8.88 (dd, 1H), 8.40 (dd, 1H), 8.21 (d, 1H), 7.91 (d, 1H), 7.82 (d, 2H), 7.75 (app d, 2H), 7.53 (dd, 1H), 7.44 (d, 1H), 7.41 (s, 1H), 7.17 (t, 1H), 7.11 (d, 1H), 4.29 (s, OH), 3.77-3.54 (m, 2H), 2.96 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.42 (s, 3H), 1.11 (s, 3H).

EXAMPLE 30

1-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-3-methyl-butane-2,3-diol



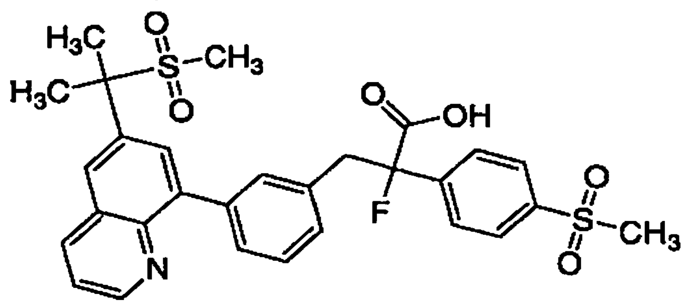
Following the procedures described in **Example 29**, but substituting **Example 17** for **Example 27** and purification by flash chromatography (eluting with toluene/acetone, 80:20 afforded the title compound as a white powder.

^{1}H NMR (400MHz, acetone-$d6$): δ 8.88 (dd, 1H), 8.40 (dd, 1H), 8.21 (d, 1H), 7.95 (d, 1H), 7.93 (d, 2H), 7.80 (d, 2H), 7.53 (dd, 1H), 7.50 (s, 1H), 7.42 (dt, 1H), 7.18-7.12 (m, 2H), 4.08 (s, OH), 4.06 (s, OH), 3.75 (d, 1H), 3.49 (d, 1H), 2.97 (s,

3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H). LRMS (CI) 582 $(M+H)^+$.

EXAMPLE 31

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid

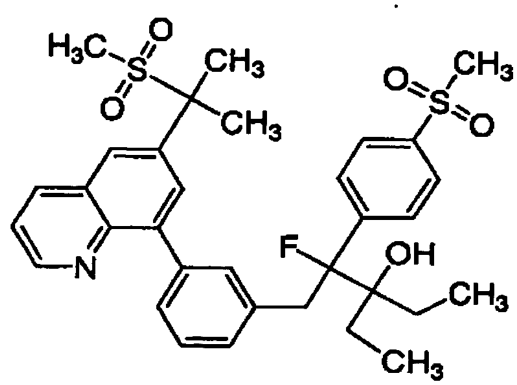


Following the procedures described in **Example 08**, but substituting **Example 27** for **Example 07** and using only 1.5 equivalent of LiOH, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, acetone-d_6): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.06 (d, 1H), 8.01 (d, 2H), 7.92 (d, 2H), 7.66 (s, 1H), 7.63 (dd, 1H), 7.56 (dd, 1H), 7.37 (t, 1H), 7.32 (d, 1H), 3.90 (dd, 1H), 3.62 (dd, 1H), 3.10 (s, 3H), 2.72 (s, 3H), 1.99 (s, 3H), 1.99 (s, 3H).

EXAMPLE 32

3-Ethyl-2-fluoro-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-pentan-3-ol

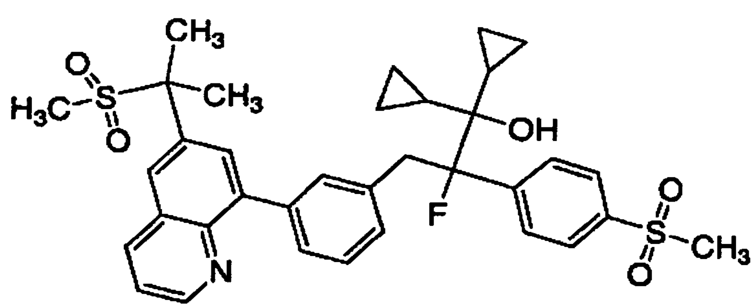


Following the procedures described above in **Example 29**, but substituting ethylmagnesium bromide for methylmagnesium bromide and purification by flash chromatography (eluting with toluene/acetone, 9:1) afforded the title compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.41 (dd, 1H), 8.21 (d, 1H), 7.92 (d, 1H), 7.81-7.75 (m, 4H), 7.54 (dd, 1H), 7.43 (d, 1H), 7.35 (s, 1H), 7.16 (t, 1H), 7.05 (d, 1H), 4.07 (s, OH), 3.75-3.59 (m, 2H), 2.93 (s, 3H), 2.71 (s, 3H), 2.01-1.90 (m, 2H), 1.98 (s, 3H), 1.97 (s, 3H), 1.45-1.32 (m, 2H), 1.02 (dt, 3H), 0.82 (dt, 3H). LRMS (CI) 612 $(M+H)^+$.

EXAMPLE 33

1,1-Dicyclopropyl-2-fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol



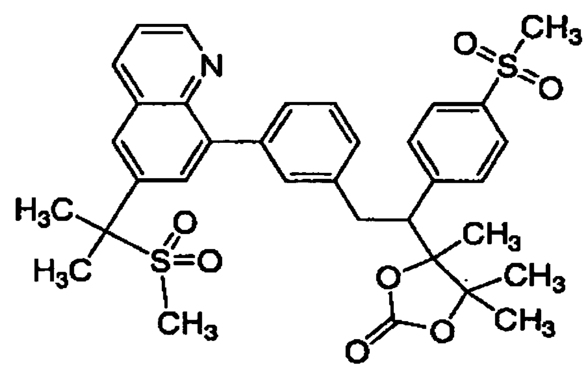
Following the procedures described above in **Example 29**, but substituting cyclopropyl magnesium bromide for methyl magnesium bromide and

purification by flash chromatography (eluting with toluene/acetone, 9:1) afforded the title compound as a white foam. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/i-PrOH/EtOH, 3:1:1, retention time 30 and 43 min) to give **Example 33A** and **Example 33B.**

^{1}H NMR (400MHz, acetone-*d6*): δ 8.89 (dd, 1H), 8.39 (dd, 1H), 8.21 (d, 1H), 7.92 (d, 1H), 7.83 (s, 4H), 7.52 (dd, 1H), 7.47 (s, 1H), 7.44 (dd, 1H), 7.18-7.16 (m, 2H), 3.94 (dd, 1H), 3.87 (dd, 1H), 3.69 (s, OH), 2.97 (s, 3H), 2.71 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.12-1.07 (m, 1H), 0.91-0.86 (m, 1H), 0.69-0.64 (m, 1H), 0.53-0.49 (m, 1H), 0.43-0.29 (m, 5H), 0.17-0.12 (m, 1H). LRMS (CI) 636 $(M+H)^+$.

EXAMPLE 34

4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethyl]-4,5,5-trimethyl-[1,3]dioxolan-2-one

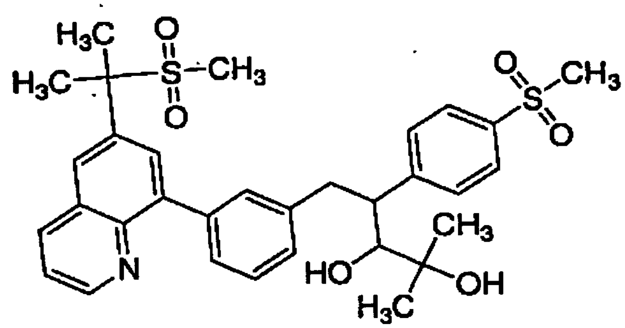


Example 10 (236mg, 0.39mmol) and CDI (650mg, 4mmol) was heated at 90°C for 18h, cooled to 21°C, and then diluted with ethyl acetate and sodium bicarbonate solution. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with dichloromethane / ethyl acetate, 40:60) provided the title compound as a white solid (245mg). The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/i-PrOH, 40:60, retention time 10.7 and 12.6 min) to give **Example 34A** and **Example 34B.**

^{1}H NMR (400MHz, acetone-*d6*): δ 8.89 (dd, 1H), 8.41 (dd, 1H), 8.21 (d, 1H), 7.95 (d, 1H), 7.86 (d, 2H), 7.78 (d, 2H), 7.59 (s, 1H), 7.54 (dd, 1H), 7.47 (d, 1H), 7.25 (t, 1H), 7.23 (d, 1H), 4.10 (dd, 1H), 3.47 (dd, 1H), 3.16 (dd, 1H), 3.06 (s, 3H), 2.71 (s, 3H), 1.96 (s, 6H), 1.87 (s, 3H), 1.71 (s, 3H), 1.48 (s, 3H).

EXAMPLE 35

5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-(4-methanesulfonyl-phenyl)-2-methyl-pentane-2,3-diol

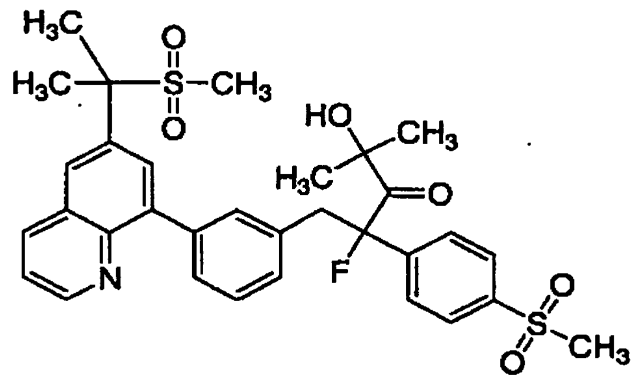


Following the procedures described above in **Example 21**, but substituting **Example 1** for **Example 6** and using THF/EtOH as solvent. Purification by flash chromatography (eluting with dichloromethane/ethyl acetate, 40:60) afforded the title compound (one pair of enantiomer).

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.06 (d, 1H), 7.75 (dd, 4H), 7.60 (s, 1H), 7.56 (dd, 1H), 7.50 (d, 1H), 7.31 (t, 1H), 7.20 (d, 1H), 4.12 (d, 1H), 3.81 (m, 1H), 3.50 (m, 1H), 3.36 (dd, 1H), 3.26 (s, 1H), 3.10 (dd, 1H), 2.99 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H), 1.03 (s, 3H), 0.87 (s, 3H).

EXAMPLE 36

2-Fluoro-4-hydroxy-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-4-methyl-pentan-3-one

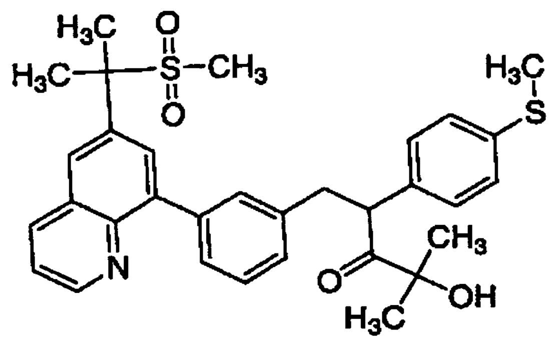


To a solution of **Example 1** (200mg, 0.34mmol) in THF/DMF (1:1, 10mL) at 0°C was added potassium tert-butoxide (1M, THF, 0.34mL, 0.34mmol) dropwise. After 15 min, N-fluorobenzene sulfonimide (212mg, 0.73mmol) was added and the reaction mixture stirred for 2h at 21°C. The resulting mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 80:20) provided the title compound.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 1H), 8.45 (dd, 1H), 8.29 (d, 1H), 8.08 (d, 1H), 7.98 (d, 2H), 7.88 (d, 2H), 7.55 (m, 3H), 7.38 (t, 1H), 7.26 (d, 1H), 4.22 (brs, 1H), 3.87 (dd, 1H), 3.42 (dd, 1H), 3.10 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H), 1.17 (s, 3H), 1.12 (s, 3H).

EXAMPLE 37

4-Hydroxy-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-methyl-2-(4-methylsulfanyl-phenyl)-pentan-3-one

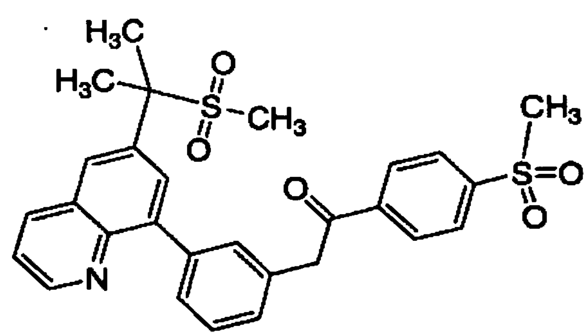


Following the procedures described in **Example 1**, but substituting **Ketone 01** for **Ketone 02** and purification by flash chromatography (eluting with ethyl acetate/hexane, 1:1 to 3:2) afforded the title compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.56 (dd, 1H), 7.51 (m, 2H), 7.33 (m, 3H), 7.2 (m, 3H), 4.94 (dd, 1H), 4.31 (s, OH), 3.38 (dd, 1H), 3.00 (dd, 1H), 2.7 (s, 3H), 2.44 (s, 3H), 1.98 (s, 6H), 1.07 (s, 3H), 1.03 (s, 3H).

EXAMPLE 38

2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanone



Step 1: (tert-Butyl-dimethyl-silanyloxy)-(4-methylsulfanyl-phenyl)-acetonitrile

To a solution of 4-methylthiobenzaldehyde (8g, 52.5mmol) in acetonitrile (260mL) was added KCN (13.7g, 210mmol), ZnI_2 (335mg, 1mmol) and t-BDMSCl (9.5g, 63mmol). After 18h, the resulting reaction mixture was filtered and

the mother liquors concentrated. The resulting residue was left overnight under high vacuum to provided the (tert-butyl-dimethyl-silanyloxy)-(4-methylsulfanyl-phenyl)-acetonitrile compound as a clear oil.

Step 2: 2-(tert-Butyl-dimethyl-silanyloxy)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionitrile

To a solution of (tert-butyl-dimethyl-silanyloxy)-(4-methylsulfanyl-phenyl)-acetonitrile from **Step 1** above (1.52g, 5.2mmol) in THF (25mL) at -78°C was added KHMDS (1M, 5.2mL, 5.2mmol) dropwise followed, after 10 min, by **Quinoline 01** (1.8g, 4.3mmol) in THF (25mL). The resulting reaction mixture was allowed to warm to -10°C and diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated.

Step 3: 2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methylsulfanyl-phenyl)-ethanone

To a solution of crude cyanohydrin from **Step 2** above in THF (25mL) was added tetrabutylammonium fluoride (1M, THF, 6.5mL, 6.5mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 30min and diluted with a sodium hydroxide solution and ethyl acetate. The organic extracts were washed (1N NaOH 2 X), (brine), dried ($MgSO_4$), filtered and concentrated.

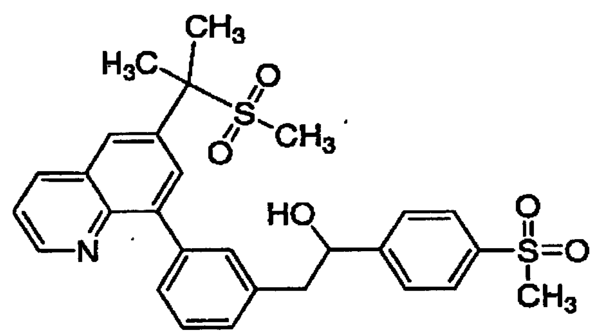
Step 4: 2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanone

Following the procedures described above in **Example 16**, but substituting the 2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methylsulfanyl-phenyl)-ethanone from step 3 for **Example 15**, the 2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanone compound was obtained as a foam.

^{1}H NMR (400MHz, acetone-d_6): δ 8.89 (dd, 1H), 8.44 (dd, 1H), 8.35 (d, 2H), 8.26 (d, 1H), 8.10-8.08 (m, 3H), 7.72 (s, 1H), 7.63 (d, 2H), 7.56 (dd, 1H), 7.44 (t, 1H), 7.38 (d, 1H), 4.57 (s, 2H), 3.17 (s, 3H), 2.70 (s, 3H), 1.98 (s, 6H).

EXAMPLE 39

2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanol

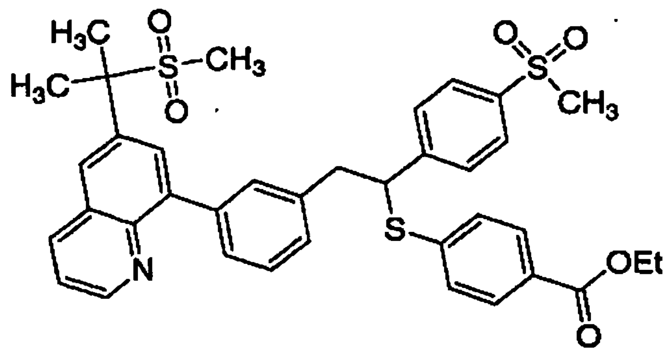


Following the procedures described above in **Example 21**, but substituting **Example 38** for **Example 6** and using THF/MeOH as solvent. The resulting residue was stirred vigorously in ethyl acetate/ether for 1h then filtered to afford the title compound as a white powder.

^{1}H NMR (400MHz, acetone-d_6): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.09 (d, 1H), 7.88 (d, 2H), 7.61-7.53 (m, 3H), 7.59 (d, 2H), 7.36 (t, 1H), 7.27 (app d, 1H), 5.62 (app t, 1H), 4.67 (d, OH), 3.11 (d, 2H), 3.06 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H).

EXAMPLE 40

4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethylsulfanyl]-benzoic acid ethyl ester

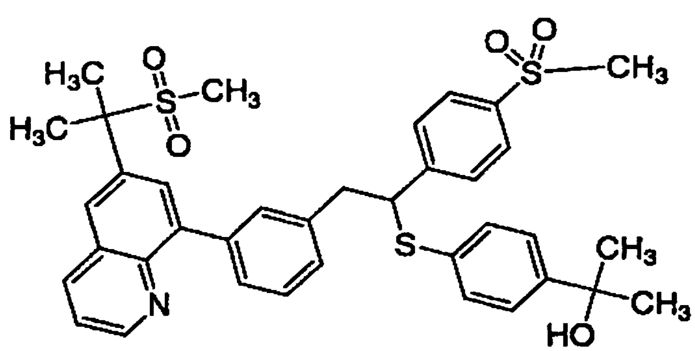


To a solution of **Example 39** (283mg, 0.54mmol), Ph_3P (283mg, 1.08mmol) and DEAD (0.17mL, 1.08mmol) in THF (3mL) at 0°C, was slowly added ethyl 4-mercaptobenzoate (200mg, 1.08mmol, over 20min.) in DMF (2mL). The reaction mixture was stirred at 0°C 1h, at 21°C for 18h, then diluted with water and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1) provided the title compound as an oil.

^{1}H NMR (400MHz, acetone-d_6): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.05 (d, 1H), 7.85-7.81 (m, 4H), 7.74 (dd, 2H), 7.62 (s, 1H), 7.58-7.55 (m, 2H), 7.45 (dd, 2H), 7.32 (t, 1H), 7.23 (d, 1H), 5.13 (dd, 1H), 4.28 (q, 2H), 3.47-3.38 (m, 2H), 3.01 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H), 1.31 (t, 3H).

EXAMPLE 41

2-{4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethylsulfanyl]-phenyl}-propan-2-ol

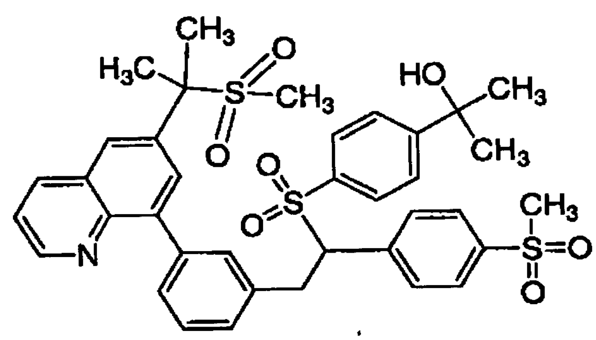


A solution of **Example 40** (280mg, 0.4mmol) and anhydrous $CeCl_3$ (150mg, 0,5mmol) in THF (5mL) was stirred at 21°C for 1h, then cooled at -78°C. Methylmagnesium bromide (3M, Ether, 0.6mL, 2.1mmol) was added and the resulting reaction mixture warmed slowly to 0°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1 to 2:8) provided the title compound as a solid.

^1H NMR (400MHz, acetone-d_6): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.24 (d, 1H), 8.04 (d, 1H), 7.79 (s, 2H), 7.71-7.53 (m, 5H), 7.41 (d, 2H), 7.32-7.28 (m, 3H), 7.19 (d, 1H), 4.88 (dd, 1H), 4.02 (s, OH), 3.45-3.34 (m, 2H), 3.01 (s, 3H), 2.71 (s, 3H), 1.97 (s, 6H), 1.44 (s, 6H).

EXAMPLE 42

2-{4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonyl]-phenyl}-propan-2-ol



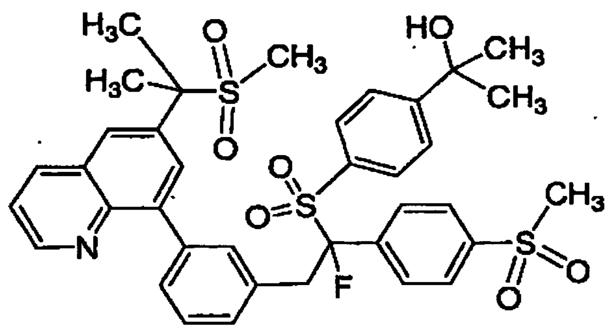
Following the procedures described above in **Example 16**, but substituting **Example 41** for **Example 15** and purification by stirring vigorously the resulting solid in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder.

^1H NMR (400MHz, acetone-d_6): δ 8.86 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.93 (d, 1H), 7.79 (d, 2H), 7.71-7.51 (m, 8H), 7.71 (d, 1H), 7.47 (d, 1H), 7.24

(t, 1H), 5.07 (dd, 1H), 4.33 (s, OH), 3.75 (dd, 1H), 3.62 (dd, 1H), 3.05 (s, 3H), 2.70 (s, 3H), 1.95 (s, 6H), 1.50 (s, 3H), 1.50 (s, 3H).

EXAMPLE 43

2-{4-[1-Fluoro-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonyl]-phenyl}-propan-2-ol

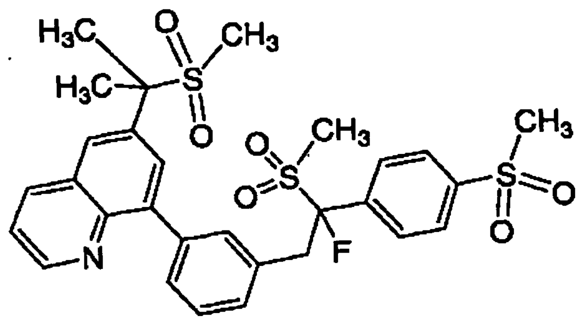


By following the procedures described above in **Example 36**, but substituting **Example 42** for **Example 1**, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, acetone-d_6): δ 8.84 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.92 (d, 1H), 7.86 (d, 2H), 7.71-7.51 (m, 9H), 7.26 (t, 1H), 7.20 (d, 1H), 4.38 (s, OH), 4.19 (dd, 1H), 3.88 (dd, 1H), 3.07 (s, 3H), 2.69 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.51 (s, 3H), 1.50 (s, 3H).

EXAMPLE 44

8-{3-[2-Fluoro-2-methanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

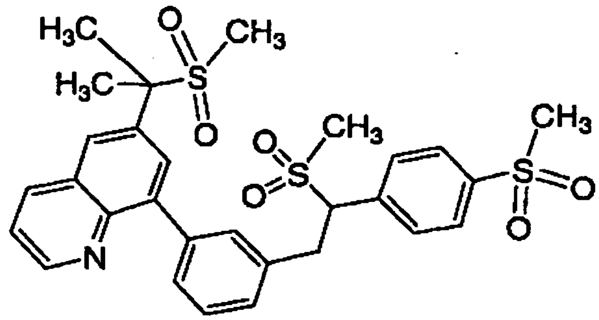


Example 44 was prepared by following the procedures described above in **Example 1**, but substituting **Sulfone 02** for **Ketone 02**, and using DMF as solvent. Purification by flash chromatography (eluting with ethyl acetate/hexane, 95:5 to 100:0), then stirring vigorously the resulting solid in ether/ethyl acetate for 1h and filtration afforded the title compound as a white powder. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH/i-PrOH/MeOH, 30:30:30:10, retention time 10.0 and 12.5 min) to give **Example 44A** and **Example 44B**.

^{1}H NMR (400MHz, ace-*d6*): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.85 (d, 2H), 7.57 (app d, 1H), 7.55 (dd, 1H), 7.50 (app d, 1H), 7.30 (t, 1H), 7.24 (app d, 1H), 5.01 (dd, 1H), 3.87 (dd, 1H), 3.55 (dd, 1H), 3.07 (s, 3H), 2.88 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 45

8-{3-[2-Methanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

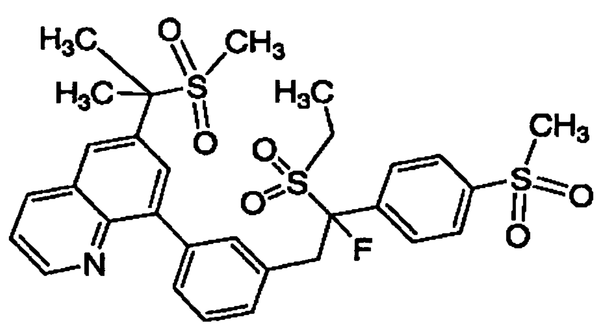


Example 45 was prepared by following the procedures described above in **Example 1**, but substituting **Sulfone 01** for **Ketone 02**, and using DMF as solvent. Purification by flash chromatography (eluting with ethyl acetate/hexane, 80:20 to 100:0), then stirring vigorously the resulting solid in ethyl acetate/ether for 1h and filtration afforded the title compound as a white powder.

^{1}H NMR (400MHz, acetone-d_6): δ 8.90 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.85 (d, 2H), 7.57 (app d, 1H), 7.55 (dd, 1H), 7.50 (d, 1H), 7.30 (t, 1H), 7.24 (d, 1H), 5.01 (dd, 1H), 3.87 (dd, 1H), 3.54 (dd, 1H), 3.07 (s, 3H), 2.88 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 46

8-{3-[2-Ethanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



Step 1: 8-{3-[2-Ethanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

The procedures described above in **Example 01** were followed, but **Sulfone 04** was substituted for **Ketone 02**, and THF was used as the solvent. Purification by flash chromatography (eluting with ethyl acetate/hexane, 80:20 to 100:0), then stirring vigorously the resulting solid in ethyl acetate/ether for 1h and filtration afforded the 8-{3-[2-ethanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline compound as a white powder.

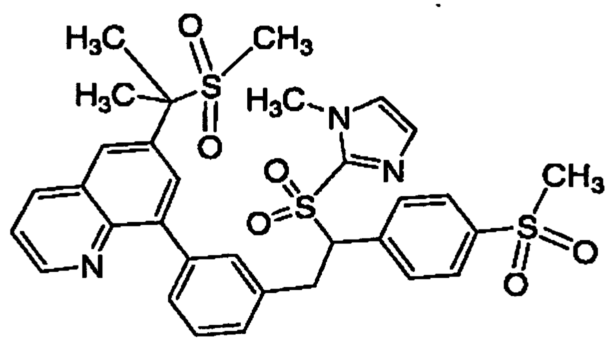
Step 2: 8-{3-[2-Ethanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

Following the procedures described in **Example 36**, but substituting 8-{3-[2-ethanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from **Step 1** above for **Example 1**, the 8-{3-[2-ethanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline compound was obtained as a white solid.

^{1}H NMR (400MHz, ace-*d6*): δ 8.89 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.01 (d, 2H), 7.96-7.92 (m, 3H), 7.57-7.53 (m, 3H), 7.29 (t, 1H), 7.21 (app d, 1H), 4.04 (m, 2H), 3.22-3.15 (m, 1H), 3.07 (s, 3H), 3.00-2.91 (m, 1H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.26 (t, 3H).

EXAMPLE 47

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[2-(4-methanesulfonyl-phenyl)-2-(1-methyl-1H-imidazole-2-sulfonyl)-ethyl]-phenyl}-quinoline

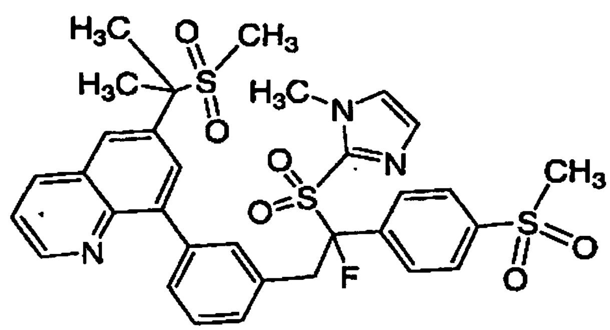


Example 47 was prepared by following the procedures described above in **Example 1**, but substituting **Sulfone 05** for **Ketone 02**, and using THF as solvent. Purification by flash chromatography (eluting with ethyl acetate), then stirring vigorously the resulting solid in ethyl acetate/ether for 1h and filtration afforded the title compound as a white powder.

^{1}H NMR (400MHz, ace-*d6*): δ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.85 (d, 2H), 7.57 (d, 1H), 7.55 (dd, 1H), 7.50 (d, 1H), 7.30 (t, 1H), 7.24 (d, 1H), 5.01 (dd, 1H), 3.87 (dd, 1H), 3.55 (dd, 1H), 3.07 (s, 3H), 2.88 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 48

8-{3-[2-Fluoro-2-(4-methanesulfonyl-phenyl)-2-(1-methyl-1H-imidazole-2-sulfonyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

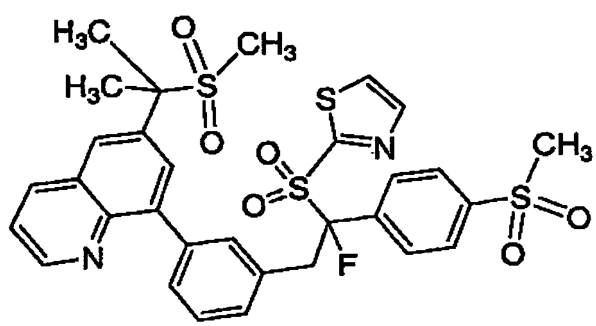


By following the procedures described above in **Example 36**, but substituting **Example 47** for **Example 1**, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, ace-*d6*): δ 8.85 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.97 (d, 2H), 7.93 (d, 1H), 7.77 (d, 1H), 7.55-7.52 (m, 3H), 7.49 (s, 1H), 7.27 (t, 1H), 7.21 (s, 1H), 7.19 (app d, 1H), 4.23 (d, 1H), 3.95 (dd, 1H), 3.79 (s, 3H), 3.11 (s, 3H), 2.70 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H).

EXAMPLE 49

8-{3-[2-Fluoro-2-(4-methanesulfonyl-phenyl)-2-(thiazole-2-sulfonyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

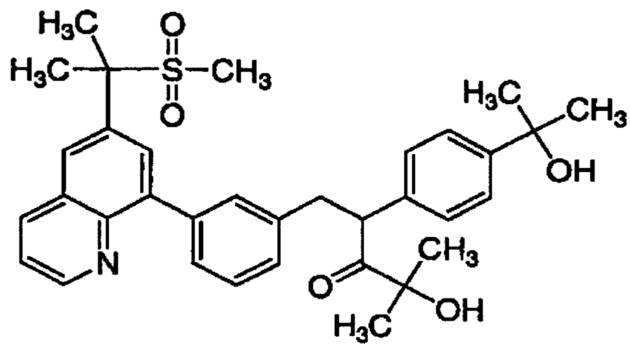


By following the procedures described above in **Example 46**, but substituting **Sulfone 06** for **Sulfone 04** in **Step 1**, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, ace-*d6*): δ 8.85 (dd, 1H), 8.41 (dd, 1H), 8.31 (d, 1H), 8.22 (d, 1H), 8.20 (d, 1H), 7.97-7.93 (m, 3H), 7.82 (d, 2H), 7.56-7.52 (m, 3H), 7.28 (t, 1H), 7.21 (app d, 1H), 4.30 (dd, 1H), 4.10 (dd, 1H), 3.09 (s, 3H), 2.70 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H.

EXAMPLE 50

4-Hydroxy-2-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-methyl-pentan-3-one

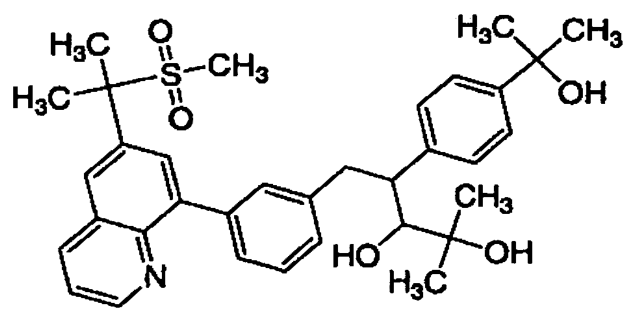


By following the procedures described above in **Example 1**, but substituting **Ketone 11** for **Ketone 02**, the title compound was obtained as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.07 (d, 1H), 7.58 (m, 2H), 7.49 (d, 1H), 7.45 (d, 2H), 7.35 (m, 3H), 7.22 (d, 1H), 4.97 (dd, 1H), 4.27 (s, OH), 3.94 (s, OH), 3.38 (dd, 1H), 2.99 (dd, 1H), 2.71 (s, 3H), 1.99 (s, 6H), 1.46 (s, 6H), 1.04 (s, 3H), 1.00 (s, 3H).

EXAMPLE 51

4-[4-(1-Hydroxy-1-methyl-ethyl)-phenyl]-5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-methyl-pentane-2,3-diol

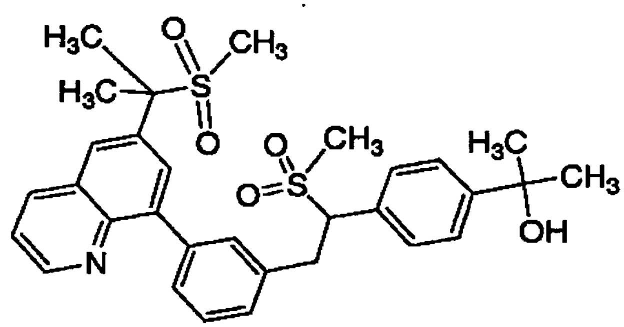


By following the procedures described above in **Example 21**, but substituting **Example 50** for **Example 6** and using EtOH as solvent, the title compound was obtained as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.93 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.09 (d, 1H), 7.65 (s, 1H), 7.56 (dd, 1H), 7.52 (d, 1H), 7.45-7.32 (m, 4H), 7.32 (t, 1H), 7.23 (d, 1H), 3.86 (s, OH), 3.71 (m, 2H), 3.30 (m, 2H), 3.01 (m, 2H), 2.71 (s, 3H), 1.99 (s, 6H), 1.45 (s, 6H), 1.05 (s, 3H), 0.78 (s, 3H).

EXAMPLE 52

2-[4-(1-Methanesulfonyl-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-ethyl)-phenyl]-propan-2-ol

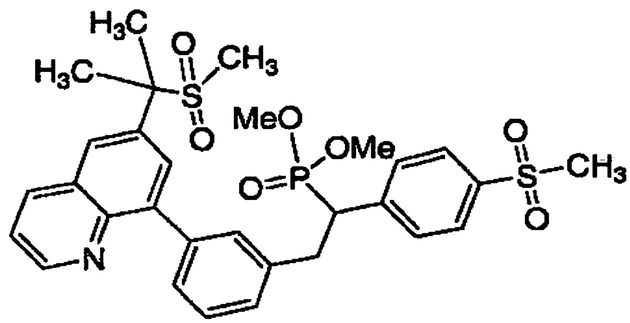


By following the procedures described above in **Example 1**, but substituting **Sulfone 07** for **Ketone 02**, the title compound was obtained as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.90 (dd, 2H), 8.42 (dd, 2H), 8.24 (d, 1H), 8.00 (d, 1H), 7.59 (s, 1H), 7.55 (dd, 1H), 7.51 (m, 5H), 7.29 (t, 1H), 7.21 (d, 1H), 4.75 (dd, 1H), 3.99 (s, OH), 3.81 (dd,), 3.49 (dd, 1H), 2.74 (s, 3H), 2.7 (s, 3H), 1.97 (s, 6H), 1.44 (s, 6H).

EXAMPLE 53

[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethyl]-phosphonic acid dimethyl ester

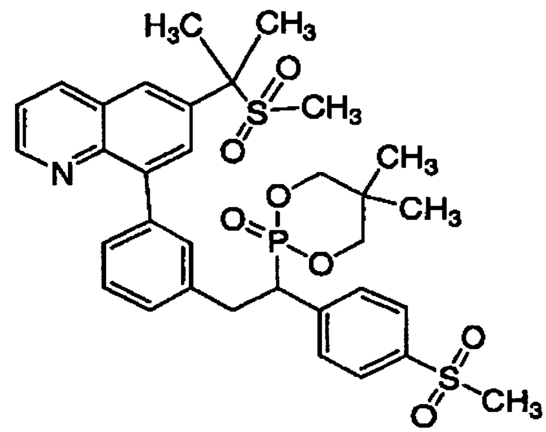


By following the procedures described above in **Example 1**, but substituting **Phosphonate 01** for **Ketone 02** and purification by flash chromatography (eluting with toluene/acetone, 50:50), the title compound was obtained as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.89 (dd, 1H), 8.40 (dd, 1H), 8.23 (d, 1H), 8.01 (d, 1H), 7.84 (d, 2H), 7.71 (d, 2H), 7.50 (m, 3H), 7.26 (s, 1H), 7.19 (d, 1H), 3.90 (m, 1H), 3.71 (d, 3H), 3.57 (d, 3H), 3.55 (m, 1H), 3.40 (m, 1H), 3.02 (s, 3H), 2.70 (s, 3H), 1.98 (s, 6H).

EXAMPLE 54

8-{3-[2-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

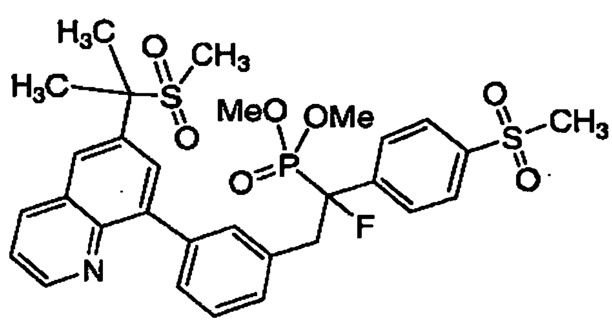


By following the procedures described above in **Example 1**, but substituting **Phosphonate 03** for **Ketone 02** and purification by flash chromatography (eluting with toluene/acetone, 60:40), the title compound was obtained as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.00 (d, 1H), 7.84 (d, 2H), 7.73 (d, 2H), 7.53 (m, 3H), 7.27 (t, 1H), 7.18 (d, 1H), 4.20 (m, 3H), 4.03 (m, 1H), 3.92 (m, 1H), 3.57 (m, 1H), 3.40 (m, 1H), 3.06 (s, 3H), 2.72 (s, 3H), 1.97 (s, 6H), 1.13 (s, 3H), 0.91 (s, 3H).

EXAMPLE 55

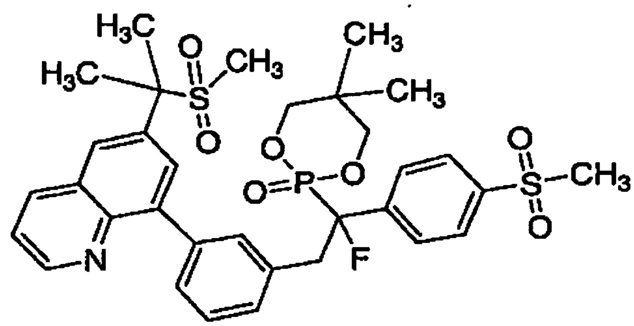
[1-Fluoro-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethyl]-phosphonic acid dimethyl ester



By following the procedures described above in **Example 1**, but substituting **Phosphonate 02** for **Ketone 02** and purification by flash chromatography (eluting with toluene/acetone, 60:40), the title compound was obtained as a white foam.54 corrected ^{1}H NMR (400MHz, acetone-*d6*): δ 8.88 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.96 (d, 1H), 7.92 (d, 2H), 7.78 (d, 2H), 7.53 (m, 2H), 7.49 (s, 1H), 7.28 (t, 1H), 7.14 (s, 1H), 3.84 (d, 3H), 3.83 (m, 2H), 3.58 (d, 3H), 3.02 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H).

EXAMPLE 56

8-{3-[2-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

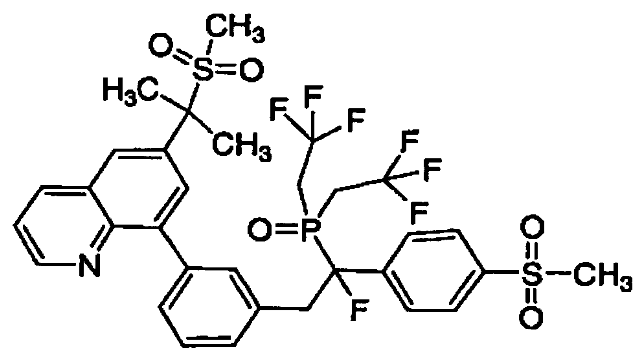


By following the procedures described above in **Example 36**, but substituting **Example 54** for **Example 1** and purification by flash chromatography (eluting with toluene/acetone, 75:25), the title compound was obtained as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.80 (d, 2H), 7.53 (m, 2H), 7.48 (s, 1H), 7.26 (t, 1H), 7.14 (d, 1H), 4.53 (dd, 1H), 4.38 (dd, 1H), 4.14 (m, 1H), 3.96 (m, 1H), 3.89 (m, 1H), 3.72 (m, 1H), 3.02 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H), 1.25 (s, 3H), 0.93 (s, 3H).

EXAMPLE 57

8-{3-[2-[Bis-(2,2,2-trifluoro-ethyl)-phosphinoyl]-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

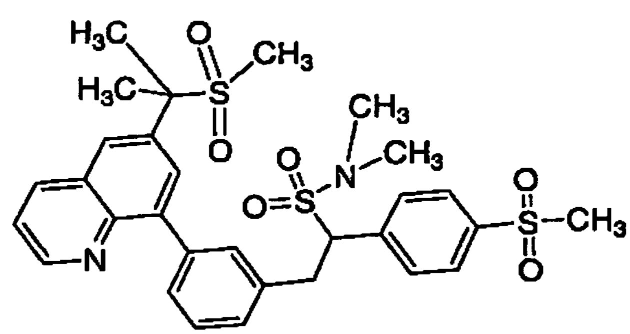


Following the procedures described above in **Example 46**, but substituting **Phosphonate 04** for **Sulfone 04** and purification by flash chromatography (eluting with toluene/acetone, 70:30), afforded the title compound as a white foam.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.45 (m, 1H), 8.29 (m, 1H), 8.25 (d, 1H), 8.10 (d, 1H), 7.95 (d, 2H), 7.85 (d, 1H), 7.59 (m, 3H), 7.33 (t, 1H), 7.27 (d, 1H), 4.78 (m, 1H), 4.59 (m, 2H), 4.39 (m, 1H), 3.85 (m, 2H), 3.05 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H).

EXAMPLE 58

2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonic acid dimethylamide

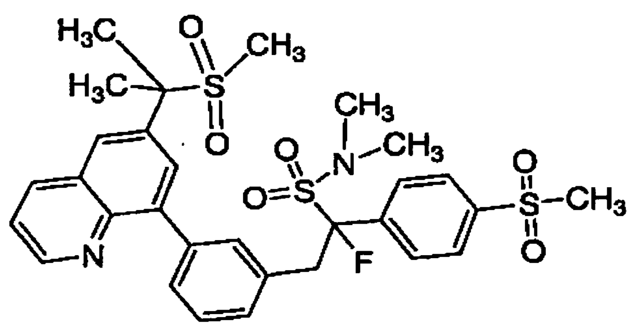


By following the procedures described above in **Example 1**, but substituting **Sulfone 08** for **Ketone 02**, the title compound was obtained as a white foam.

^{1}H NMR (400MHz, acetone-d_6): δ 8.88 (dd, 1H), 8.39 (dd, 1H), 8.22 (d, 1H), 7.97 (d, 1H), 7.93 (d, 2H), 7.86 (d, 2H), 7.55-7.50 (m, 3H), 7.29-7.19 (m, 2H), 5.03 (dd, 1H), 3.75 (dd, 1H), 3.57 (dd, 1H), 3.05 (s, 3H), 2.70 (s, 3H), 2.67 (s, 6H), 1.96 (s, 6H).

EXAMPLE 59

1-Fluoro-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonic acid dimethylamide

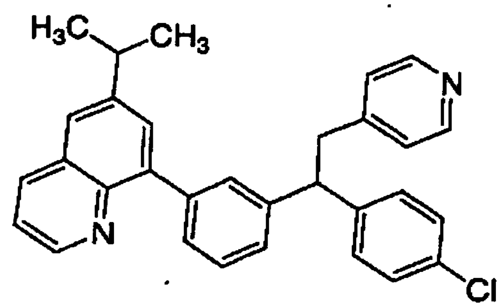


By following the procedures described above in **Example 36**, but substituting **Example 58** for **Example 1**, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, acetone-d_6): δ 8.98 (d, 1H), 8.88 (dd, 1H), 8.18 (dd, 1H), 7.90 (d, 2H), 7.81 (d, 3H), 7.48 (d, 1H), 7.41 (dd, 1H), 7.39 (s, 1H), 7.25 (t, 1H), 7.07 (d, 1H), 3.96-3.80 (m, 2H), 2.95 (s, 3H), 2.68 (br s, 6H), 2.60 (s, 3H), 1.944 (s, 3H), 1.936 (s, 3H).

EXAMPLE 60

8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-isopropyl-quinoline



Step 1: (4-Chloro-phenyl)-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol

To a solution of **Quinoline 04** (1.0g, 3.6mmol) in CH_2Cl_2 (5mL) at -10°C was added 4-chlorophenylmagnesium bromide (0.7M, THF, 5mL, 7mmol) dropwise. After 1h, a saturated ammonium chloride solution was added and the reaction mixture extracted with CH_2Cl_2 (3X). The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the (4-chloro-phenyl)-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol compound as a white solid.

Step 2: 8-{3-[Chloro-(4-chloro-phenyl)-methyl]-phenyl}-6-isopropyl-quinoline

To a solution of (4-chloro-phenyl)-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol from **Step 1** (1.0g, 2.58mmol) in benzene (7mL) at 0°C was added $SOCl_2$ (0.375mL, 5.2mmol) dropwise. After 45min. at 0-10°C, the resulting reaction mixture was filtered throu gh silica gel and celite and then concentrated.

Step 3: 3-(4-Chloro-phenyl)-3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionic acid ethyl ester

To a solution of ethyl 4-pyridinylacetate (1.28g, 7.74mmol) in THF/HMPA (3:1, 5mL) at -10°C was added NaHMDS (1M, 7.8mL, 7.8mmol) dropwise. After 60min., the crude chloride from **Step 2** above was added and the resulting reaction mixture was stirred for 18h at 21°C, and then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated.

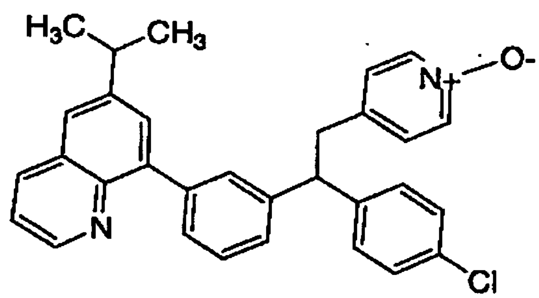
Step 4: 8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-isopropyl-quinoline

To a solution of the crude ester from **Step 3** above in THF/EtOH (10mL) was added NaOH (2N, 2mL). The resulting reaction mixture was stirred 18h at 100°C then neutralized with HCl 6N to pH 7 and diluted with ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1) provided the 8-{3-[1-(4-chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-isopropyl-quinoline compound.

^{1}H NMR (500MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.36 (d, 2H), 8.30 (dd, 1H), 7.76 (d, 2H), 7.6 (s, 1H), 7.51 (d, 1H), 7.46 (m, 3H), 7.33 (m, 4H), 7.22 (d, 2H), 4.53 (t, 1H), 3.52 (m, 2H), 3.15 (m, 1H), 1.39 (s, 6H).

EXAMPLE 61

8-{3-[1-(4-Chloro-phenyl)-2-(1-oxy-pyridin-4-yl)-ethyl]-phenyl}-6-isopropyl-quinoline

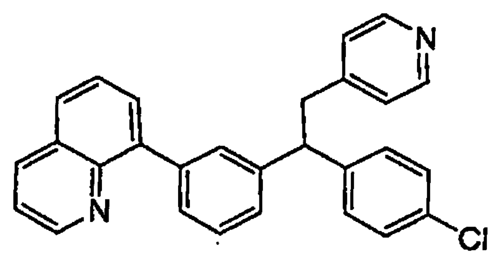


To a solution of **Example 60** (100mg, 0.22mmol) in CH_2Cl_2/MeOH (1:1, 6mL) was added MMPP (320mg, 0.65mmol). After 18h, the resulting reaction mixture was diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with ethanol/ethyl acetate, 10:90 to 25:75) provided the title compound.

^{1}H NMR (500MHz, acetone-$d6$): δ 8.83 (dd, 1H), 8.30 (dd, 1H), 7.95 (d, 2H), 7.76 (d, 2H), 7.63 (s, 1H), 7.48 (m, 4H), 7.35 (m, 4H), 7.22 (d, 2H), 4.49 (t, 1H), 3.52 (m, 2H), 3.18 (m, 1H), 1.39 (s, 6H).

EXAMPLE 62

8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-quinoline



Step 1: 4-[2-(3-Bromo-phenyl)-2-(4-chloro-phenyl)-ethyl]-pyridine

Following the procedures described above in **Example 60**, but substituting 3-bromobenzaldehyde for **Quinoline 04** and purification by flash chromatography (eluting with hexane/ethyl acetate, 4:1) afforded the 4-[2-(3-bromo-phenyl)-2-(4-chloro-phenyl)-ethyl]-pyridine compound.

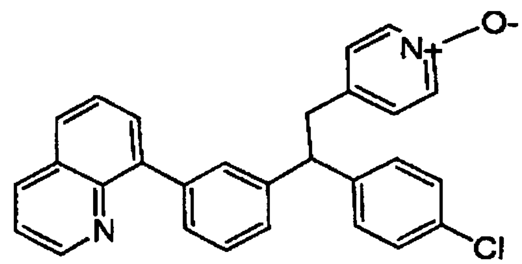
Step 2: 8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-quinoline

A solution of 4-[2-(3-bromo-phenyl)-2-(4-chloro-phenyl)-ethyl]-pyridine from **Step 1** above (400mg, 1.07mmol), diboron pinacol ester (300mg, 1.18mmol), KOAc (315mg, 3.2mmol) and $PdCl_2$(dppf) (26mg, 0.032mmol) in DMF (20mL) was heated at 80°C under N_2 for 5h. The resulting reaction mixture was cooled to 21°C, 8-bromoquinoline (290mg, 1.4mmol), Na_2CO_3 (2M, 1.61mL, 3.2mmol) and $PdCl_2$(dppf) (26mg, 0.032mmol) was then added. The reaction mixture was stirred 18h at 80°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50 to 25:75) provided the 8-{3-[1-(4-chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-quinoline compound (319mg).

^{1}H NMR (500MHz, acetone-*d6*): δ 8.88 (dd, 1H), 8.37(d, 1H), 8.36(d, 2H), 7.95 (dd, 1H), 7.76 (s, 1H), 7.71 (dd, 1H), 7.64 (t, 1H), 7.52 (m, 2H), 7.48 (d, 2H), 7.37 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 4.51 (t, 1H), 3.52 (m, 2H).

EXAMPLE 63

8-{3-[1-(4-Chloro-phenyl)-2-(1-oxy-pyridin-4-yl)-ethyl]-phenyl}-quinoline

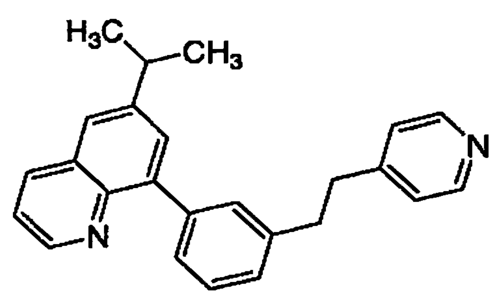


Following the procedures described above in **Example 61**, but substituting **Example 62** for **Example 60**, the title compound was obtained.

^{1}H NMR (500MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.38(dd, 1H), 7.94(m, 3H), 7.72 (t, 2H), 7.65 (t, 1H), 7.52 (m, 2H), 7.48(d, 2H), 7.32 (m, 4H), 7.21 (d, 2H), 4.48 (t, 1H), 3.50 (m, 2H).

EXAMPLE 64

6-Isopropyl-8-[3-(2-pyridin-4-yl-ethyl)-phenyl]-quinoline

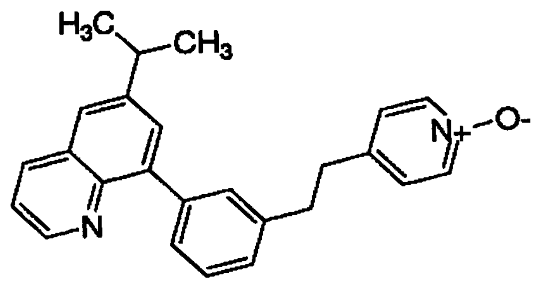


Using 3-bromobenzyl chloride as the starting material, and following the procedures described above in **Example 60, Steps 3** and **4**, followed by procedures described in **Example 62, Step 2**, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.80 (dd, 1H), 8.44 (dd, 2H), 8.29 (dd, 1H), 7.76 (d, 1H), 7.63 (d, 1H), 7.52 (s, 2H), 7.46 (q, 1H), 7.25 (t, 1H), 7.25 (d, 3H), 3.16 (m, 1H), 3.01 (s, 4H), 1.38 (d, 6H).

EXAMPLE 65

6-Isopropyl-8-{3-[2-(1-oxy-pyridin-4-yl)-ethyl]-phenyl}-quinoline

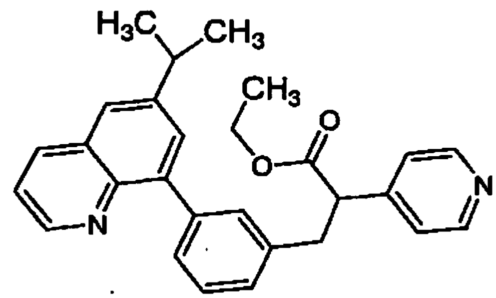


Following the procedures described in **Example 61**, but substituting **Example 64** for **Example 60**, the title compound was obtained.

^{1}H NMR (500MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 8.01 (d, 2H), 7.76 (d, 1H), 7.65 (d, 1H), 7.52 (s&dd, 2H), 7.48 (q, 1H), 7.36 (t, 1H), 7.24 (d, 3H), 3.17 (m, 1H), 3.01 (s, 4H), 1.36 (s, 6H).

EXAMPLE 66

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionic acid ethyl ester

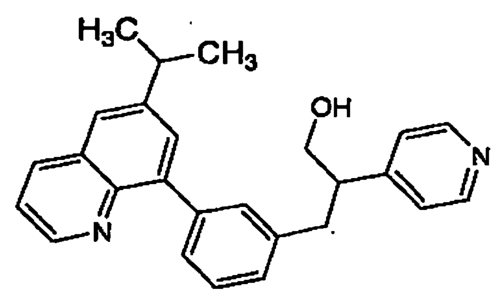


Using 3-bromobenzyl chloride as the starting material, and following the procedures described in **Example 60, Step 3**, followed by procedures described in **Example 62, Step 2**, the title compound was obtained as an oil.

^{1}H NMR (500MHz, acetone-*d6*): δ 8.82 (s, 1H), 8.52 (d, 2H), 8.28 (dd, 1H), 7.78 (d, 1H), 7.58 (d, 2H), 7.49 (t, 2H), 7.38 (m, 3H), 7.21 (d, 1H), 4.05 (q, 1H), 3.48 (q, 2H), 3.1 (q, 2H), 1.38 (d, 6H), 1.1 (t, 3H).

EXAMPLE 67

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propan-1-ol

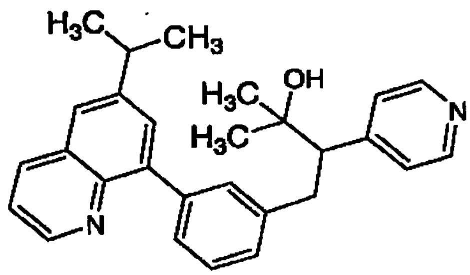


To a solution of **Example 66** (15mg, 0.035mmol) in THF (mL) at 0°C was added $LiAlH_4$ (1M, THF, 0.35mL, 0.35mmol) dropwise. The resulting reaction mixture was stirred 1h at 0°C, 1h at 21°C, and then quenched with water and neutralized using 1N HCl. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with ethanol/ethyl acetate, 1:9) provided the title compound.

^{1}H NMR (400MHz, acetone-$d6$): δ 8.78 (dd, 1H), 8.33 (dd, 1H), 7.76 (d, 1H), 7.49 (q, 1H), 7.45 (d, 1H), 7.42 (d, 1H), 7.29 (t, 4H), 7.13 (d, 1H), 4.78 (t, 1H), 3.6 (m, 2H), 3.16 (m, 3H), 2.92 (q, 1H), 1.31 (s, 6H).

EXAMPLE 68

4-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-butan-2-ol

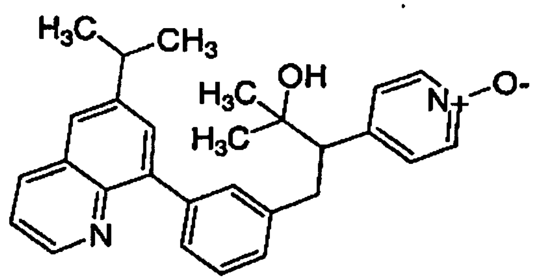


To a solution of **Example 66** (750mg, 1.77mmol) in THF (40mL) at 0°C was added methylmagnesium iodide (3M, THF, 12mL, 35mmol) dropwise. The reaction mixture was stirred 3h at 0°C, then quenched with a saturated ammonium chloride solution. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1) provided the title compound.

^{1}H NMR (400MHz, acetone-$d6$): δ 8.77 (dd, 1H), 8.39 (dd, 2H), 8.27 (dd, 1H), 7.71 (d, 1H), 7.45 (q, 1H), 7.41 (d, 2H), 7.30 (d, 3H), 7.18 (t, 1H), 7.08 (d, 1H), 3.73 (s, 1H), 3.51 (dd, 1H), 3.16 (m, 2H), 3.03 (dd, 1H), 1.36 (d, 6H), 1.28 (s,3H), 1.19 (s, 3H).

EXAMPLE 69

4-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-(1-oxy-pyridin-4-yl)-butan-2-ol

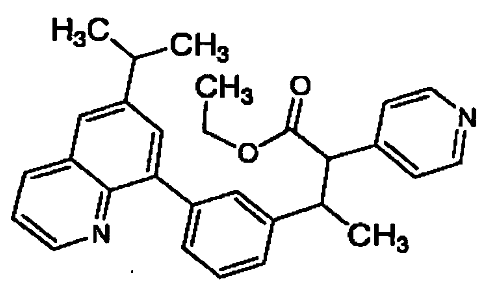


Following the procedures described in **Example 61**, but substituting **Example 68** for **Example 60**, the title compound was obtained.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.27 (dd, 1H), 7.96 (d, 2H), 7.73 (dd, 1H), 7.51 (d, 1H), 7.44 (q, 1H), 7.38 (m, 2H), 7.31 (d, 2H), 7.22 (t, 1H), 7.09 (d, 1H), 3.84 (s, 1H), 3.48 (d, 1H), 3.15 (m, 3H), 1.36 (t, 9H), 1.18 (s, 3H).

EXAMPLE 70

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-butyric acid ethyl ester

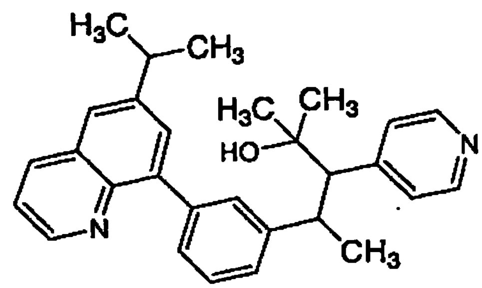


Following the procedures described in **Example 60, Steps 1-3,** but substituting methylmagnesium iodide for 4-chlorophenylmagnesium bromide, the title compound was obtained as a mixture of diastereoisomer.

^{1}H NMR (500MHz, acetone-d_6): δ 8.83 (dd, 1H), 8.36 (dd, 2H), 8.26 (dd, 1H), 7.72 (d, 1H), 7.42 (m, 4H), 7.31 (dd, 2H), 7.22 (t, 1H), 7.13 (d, 1H), 4.21 (m, 3H), 3.95 (d, 1H), 3.58 (m, 1H), 3.12 (m, 1H), 1.48 (d, 3H), 1.36 (d, 6H), 1.18 (t, 2H).

EXAMPLE 71

4-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-pentan-2-ol

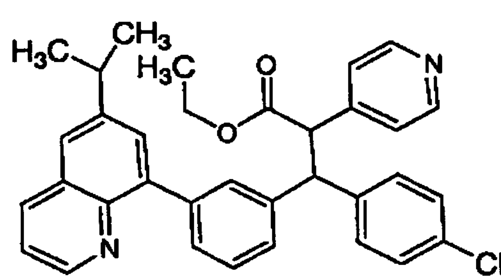


Following the procedures described in **Example 68**, but substituting **Example 70** for **Example 66**, the title compound was obtained as a mixture of diastereoisomers.

[1]H NMR (400MHz, acetone-*d6*): δ 8.83 (dd, 1H), 8.34 (dd, 2H), 8.27 (dd, 1H), 7.79 (d, 1H), 7.49 (m, 2H), 7.42 (d, 1H), 7.38 (dd, 2H), 7.28 (dd, 2H), 7.18 (d, 1H), 4.39 (s, 1H), 3.58 (m, 1H), 3.12 (m, 1H), 2.88 (d, 1H), 1.35 (d, 6H), 1.21 (s, 3H), 1.05 (d, 3H), 0.9 (s, 3H).

EXAMPLE 72

4-(4-Chloro-phenyl)-4-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-butan-2-ol



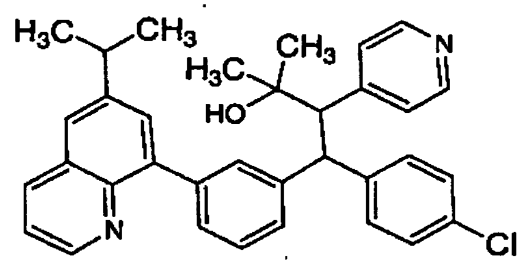
Following the procedures described in **Example 60, Steps 1-3**, the title compound was obtained as a mixture of diastereoisomers.

Isomer A: ^{1}H NMR (400MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.48 (d, 2H), 8.31 (dd, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.58 (d, 1H), 7.52 (d, 1H), 7.48 (q, 1H), 7.41 (m, 6H), 7.18 (d, 1H), 4.92 (d, 1H), 4.81 (d, 1H), 4.02 (m, 2H), 3.12 (m, 1H), 1.39 (d, 6H), 0.92 (t, 3H).

Isomer B: ^{1}H NMR (500MHz, acetone-d_6): δ 8.81 (dd, 1H), 8.48 (d, 1H), 8.42 (dd, 1H), 8.31 (m, 2H), 7.72 (d, 1H), 7.68 (d, 1H), 7.62 (d, 1H), 7.52 (d, 2H), 7.43 (m, 3H), 7.35 (d, 2H), 7.21 (t, 1H), 7.15 (d, 1H), 4.95 (d, 1H), 4.78 (d, 1H), 3.98 (m, 2H), 3.11 (m, 1H), 1.37(d, 6H), 0.95 (t, 3H).

EXAMPLE 73

4-(4-Chloro-phenyl)-4-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-butan-2-ol

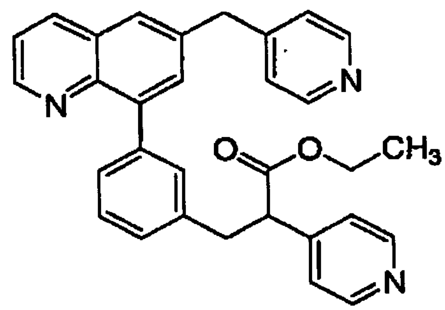


Following the procedures described in **Example 68**, but substituting **Example 72** for **Example 66**, the title compound was obtained as a mixture of diastereoisomer.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.48 (d, 2H), 8.31 (dd, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.58 (d, 1H), 7.52 (d, 1H), 7.48 (q, 1H), 7.41 (m, 6H), 7.18 (d, 1H), 5.0(d, 1H), 4.02 (d, 1H), 3.15(m, 1H), 1.38(m 9H), 1.1(t, 3H).

EXAMPLE 74

2-Pyridin-4-yl-3-[3-(6-pyridin-4-ylmethyl-quinolin-8-yl)-phenyl]-propionic acid ethyl ester

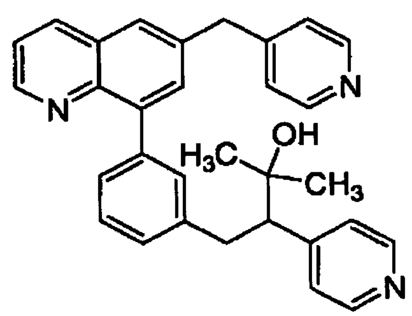


Using procedures described in **Example 60, Step 3**, but using 3-bromobenzyl chloride as the starting material, followed by the procedures described in **Example 62, Step 2**, but substituting 8-bromo 6-[(4-pyridinyl)methyl]quinoline for 8-bromoquinoline, the title compound was obtained as a oil.

^{1}H NMR (500MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.46 (q, 4H), 8.30 (dd, 1H), 7.81 (s, 1H), 7.50 (s, 1H), 7.48 (m, 2H), 7.44 (s, 1H), 7.34 (m, 5H), 7.22 (d, 1H), 4.25 (s, 2H), 4.05 (m, 3H), 3.44 (dd, 1H), 3.13 (dd, 1H), 1.07 (t, 3H).

EXAMPLE 75

2-Methyl-3-pyridin-4-yl-4-[3-(6-pyridin-4-ylmethyl-quinolin-8-yl)-phenyl]-butan-2-ol

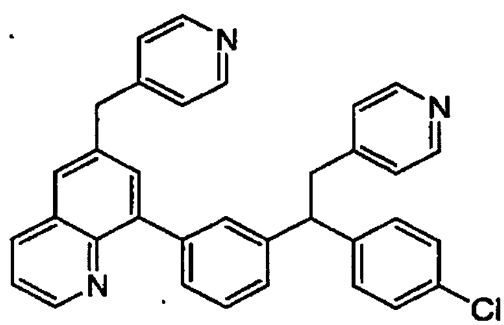


Following the procedures described in **Example 68**, but substituting **Example 74** for **Example 66**, the title compound was obtained.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.48 (dd, 2H), 8.36 (dd, 2H), 8.27 (dd, 1H), 7.76 (d, 1H), 7.48 (q, 1H), 7.34 (m, 5H), 7.28 (d, 2H), 7.18 (t, 1H), 7.05 (d, 1H), 4.23 (s, 2H), 3.48 (dd, 1H), 3.11 (m, 2H), 1.32 (s, 3H), 1.14 (s, 3H).

EXAMPLE 76

8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-pyridin-4-ylmethyl-quinoline

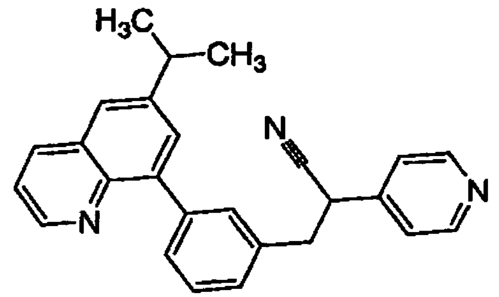


Following the procedures described in **Example 62**, but substituting 8-bromo-6-pyridin-4-ylmethyl-quinoline for 8-bromoquinoline and purification by flash chromatography (eluting with ethyl acetate/EtOH, 10:0 to 9:1) afforded the title compound.

^{1}H NMR (500MHz, acetone-*d6*): δ 8.84 (dd, 1H), 8.48 (dd, 2H), 8.35 (dd, 2H), 8.29 (dd, 1H), 7.81 (d, 1H), 7.68 (s, 1H), 7.51 (d, 1H), 7.45 (m, 2H), 7.40 (d, 2H), 7.32 (dd, 4H), 7.27 (d, 2H), 7.20 (dd, 2H), 4.50 (t, 1H), 4.24 (s, 2H), 3.47 (m, 2H).

EXAMPLE 77

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionitrile



Step 1: 3-(3-Bromo-phenyl)-2-pyridin-4-yl-propionitrile

The procedures described in **Example 60, Step 3,** were followed but substituting 4-pyridinylacetonitrile for ethyl 4-pyridinylacetate and using 3-bromobenzyl chloride as the starting material.

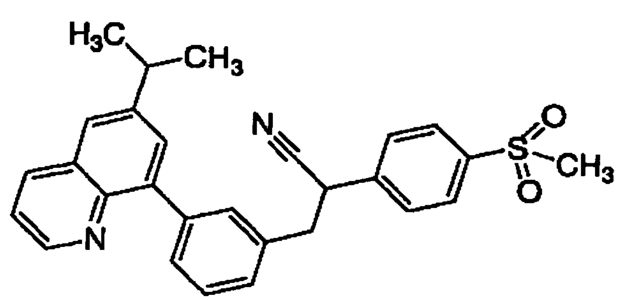
Step 2: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionitrile

Following the procedures described in **Example 62, Step 2,** but substituting 8-bromo-6-isopropylquinoline for 8-bromoquinoline and purification by flash chromatography (eluting with ethylacetate/hexane, 75:25) afforded the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionitrile compound.

^{1}H NMR (500MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.60 (dd, 2H), 8.30 (dd, 1H), 7.76 (d, 1H), 7.65 (d, 1H), 7.60 (d, 1H), 7.54 (s, 1H), 7.47 (q, 1H), 7.43 (dd, 2H), 7.39 (t, 1H), 7.29 (d, 1H), 4.56 (t, 1H), 3.36 (d, 2H), 3.16 (m, 1H), 1.37 (s, 6H).

EXAMPLE 78

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionitrile



Step 1: (4-Methanesulfonyl-phenyl)-acetonitrile

To a solution of 4-methanesulfonylbenzyl chloride (10g, 49mmol) in DMF (100mL) was added HMPA (9.35mL, 54mmol) and KCN (3.5g, 54mmol). The resulting reaction mixture was stirred 18h at 80°C, then diluted with water and ethyl acetate. The organic extracts were washed ($NaHCO_3$, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1 to 25:75) provided the (4-methanesulfonyl-phenyl)-acetonitrile compound.

Step 2:

3-[3-(6-Isopropylquinolin-8-yl)-phenyl]-2-[4-(methylsulfonyl)-phenyl]-prop-2-enenitrile

A solution of **Quinoline 04** (5g, 18mmol), 4-methanesulfonylacetonitrile (3.5g, 18mmol) from **Step 1** and piperidine (0.1mL) in toluene (5mL) was heated at 130°C. After 6h, the mixture was cooled to 21°C and purified by flash chromatography (eluting with ethylacetate/hexane, 1:1 to 75:25) to afforded the title compound.

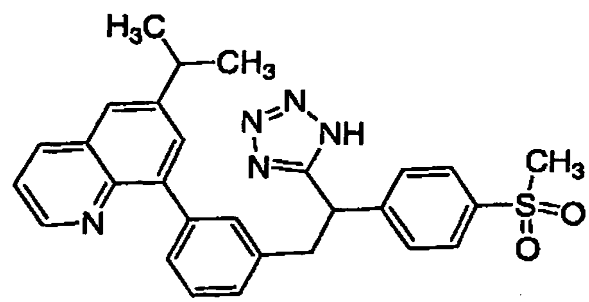
Step 3: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionitrile

A solution of the nitrile from **Step 2** (400mg, 0.88mmol) in THF/EtOH (1:1, 10mL) containing Pd/C (10%, 40mg) was stirred under H_2 (1 atm) for 3 days. Filtration on celite, evaporation, stirring vigorously in ether for 1h then filtration afforded the 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionitrile compound as a white powder.

^{1}H NMR (500MHz, acetone-d_6): δ 8.81 (dd, 1H), 8.31 (dd, 1H), 7.97 (d, 2H), 7.78 (s, 1H), 7.76 (d, 2H), 7.68 (s, 1H), 7.64 (d, 2H), 7.46 (q, 1H), 7.40 (t, 1H), 7.29 (d, 1H), 4.68 (t, 1H), 3.42 (dd, 2H), 3.15 (m, 1H), 3.08 (s, 3H), 1.38 (s, 6H).

EXAMPLE 79

6-Isopropyl-8-{3-[2-(4-methanesulfonyl-phenyl)-2-(1H-tetrazol-5-yl)-ethyl]-phenyl}-quinoline

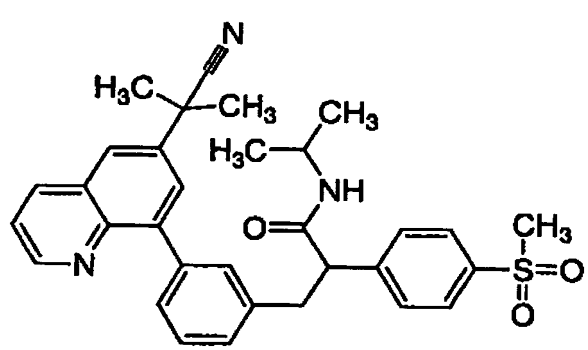


A solution of **Example 78** (160mg, 0.35mmol), tri-n-butyltin chloride (0.478mL, 1.76mmol) and sodium azide (115mg, 1.76mmol) in xylene (5mL) was heated at 150°C for 18h. Cooling to 21°C, then purification by flash chromatography (eluting with CH_2Cl_2/MeOH, NH_4OH, 50:5:1) followed by stirring vigorously in ether for 1h, then filtered, afforded the title compound as a white powder.

^{1}H NMR (500MHz, acetone-d_6): δ 8.88 (d, 1H), 8.42 (d, 1H), 7.91 (d, 2H), 7.83(s, 1H), 7.81 (d, 2H), 7.64 (dd, 2H), 7.56 (q, 1H), 7.49 (d, 1H), 7.29 (t, 1H), 7.12 (d, 1H), 5.13 (q, 1H), 3.68 (q, 1H), 3.54 (q, 1H), 3.21 (m, 1H), 3.06 (s, 3H), 1.38 (d, 6H).

EXAMPLE 80

3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-propionamide



Step 1: (E)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid

To a solution of 3-bromobenzaldehyde (12.9g, 70mmol) in toluene (100mL) was added 4-(methylsulfonyl)phenylacetic acid (15g, 70mmol) and piperidine (2mL). After overnight refluxing, the mixture was cooled down to r.t. To the slurry thus formed, toluene was added (10mL). Filtration gave the (E)-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid as a white solid.

Step 2: (E)-N-Isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

To a solution of (E)-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid from **Step 1** (24.9g, 65mmol) in toluene (250mL) was added thionyl chloride (14.3mL, 196mmol) and triethylamine (34mL, 245mmol). After stirring at 21°C for 0.5h., isopropyl amine (28mL, 327mmol) was added. After a further 2h at r.t., the mixture was cooled to 0°C and was neutralised with saturated NH_4Cl solution, then extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 1:1 to pure EtOAc) yielded the (E)-N-isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide compound.

Step 3: 3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-acrylamide

Following the procedures described above in **Example 62**, **Step 2**, but substituting **Quinoline 08** for 8-bromoquinoline and purification by flash chromatography (eluting with ethylacete/hexane, 75:25) afforded the 3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-acrylamide compound.

Step 4: 3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-propionamide

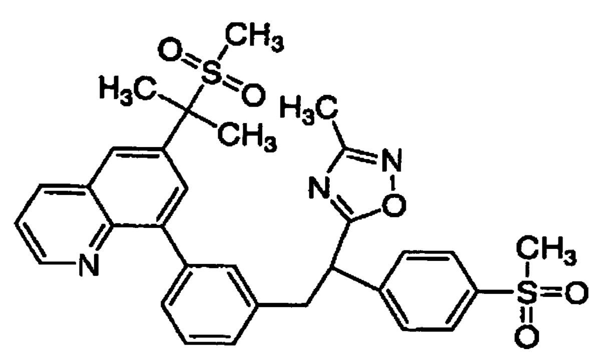
A solution of 3-{3-[6-(cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-acrylamide from **Step 3** (20mg, 0.038mmol) in THF (1mL) containing Pd/C (10%, 9mg) was stirred under H_2 (50 psi) for 18h. Filtration on celite, evaporation, and purification on HPLC (u-porasil ethyl acetate/hexane, 70:30 to 100:0, over 30min.) afforded the 3-{3-[6-(cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-propionamide compound as a foam.

Example 80 can also be prepared according to the procedure described in **Example 1** but using **Quinoline 09** and **Ester 05** as the starting material. After flash chromatography (hexane/EtOAc 50:50), the residue was stirred vigorously in ether for 1h then filtered to afford the 3-{3-[6-(cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-propionamide compound as a white powder.

^{1}H NMR (500MHz, acetone-d_6): δ 8.92 (dd, 1H), 8.46 (d, 1H), 8.11 (d, 1H), 7.86 (d, 3H), 7.72 (d, 2H), 7.65 (s, 1H), 7.58 (q, 1H), 7.51 (d, 1H), 7.35 (t, 1H), 7.28 (d, 1H), 7.12 (d, 1H), 3.96 (t, 1H), 3.85 (m, 1H), 3.51 (t, 1H), 3.07 (m, 4H), 1.85 (s, 6H), 0.93 (d, 3H), 0.88 (d, 3H).

EXAMPLE 81

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[2-(4-methanesulfonyl-phenyl)-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl}-quinoline

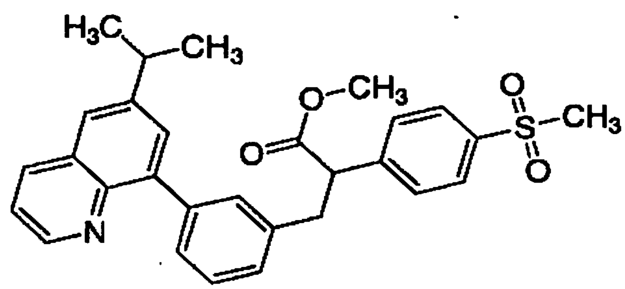


Example 81 was prepared according to the procedure described above in **Example 1** but using **Quinoline 01** and **Ester 06** as the starting material and the reaction performed from -78°C to 21°C. Flash chromatography (hexane/EtOAc 50:50 to 10:90) afforded the title compound.

^{1}H NMR (500MHz, acetone-d_6): δ 8.91 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.01 (d, 1H), 7.90 (d, 2H), 7.74 (d, 2H), 7.60 (s, 1H), 7.54 (m, 2H), 7.33 (t, 1H), 7.25 (d, 1H), 4.97 (t, 1H), 3.73 (q, 1H), 3.48 (q, 1H), 3.06 (s, 3H), 2.70 (s, 3H), 2.31 (s, 3H), 1.96 (d, 6H).

EXAMPLE 82

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester



Step 1: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester

Following the procedures described in **Example 13, Step 1**, but substituting **Quinoline 06** for **Quinoline 01**, the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester compound was obtained as a white foam.

Step 2: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester

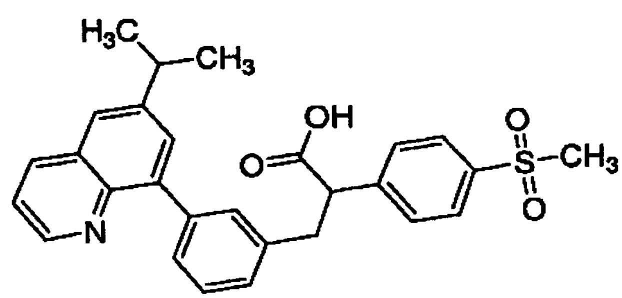
A solution of 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester from **Step 1** (1.05g, 2.3mmol),

NMO (655mg, 4.85mmol) and OsO_4 (4%, H_2O, 1mL, 0.16mmol) in THF (20mL) was stirred 18h at 21°C. The resulting reaction mixture was diluted with a sodium metabisulfite solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20) provided the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester compound.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.29 (dd, 1H), 7.89 (dd, 2H), 7.76 (d, 1H), 7.67 (d, 2H), 7.63 (d, 1H), 7.56-7.53 (m, 2H), 7.46 (dd, 1H), 7.32 (t, 1H), 7.21 (d, 1H), 4.23 (t, 1H), 3.61 (s, 3H), 3.54 (dd, 1H), 3.19-3.13 (m, 2H), 3.06 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H). LRMS (CI) 488 $(M+H)^+$.

EXAMPLE 83

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid

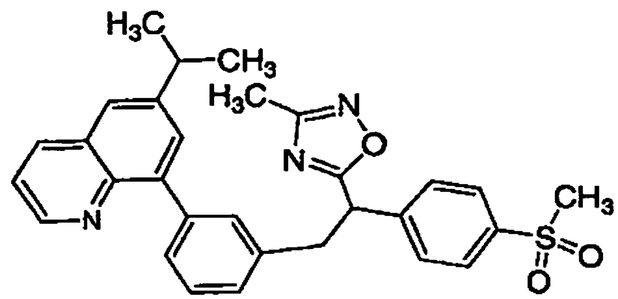


Following the procedures described in **Example 8**, but substituting **Example 82** for **Example 7**, the title compound was obtained as a white solid.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.29 (dd, 1H), 7.98 (d, 2H), 7.76 (s, 1H), 7.70 (d, 2H), 7.64 (dd, 1H), 7.59 (s, 1H), 7.54 (d, 1H), 7.47 (dd, 1H), 7.32 (t, 1H), 7.24 (d, 1H), 4.22 (t, 1H), 3.53 (dd, 1H), 3.20-3.13 (m, 2H), 3.07 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H). LRMS (CI) 474 $(M+H)^+$ 430 $(M+H - COOH)^+$.

EXAMPLE 84

6-Isopropyl-8-{3-[2-(4-methanesulfonyl-phenyl)-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl}-quinoline

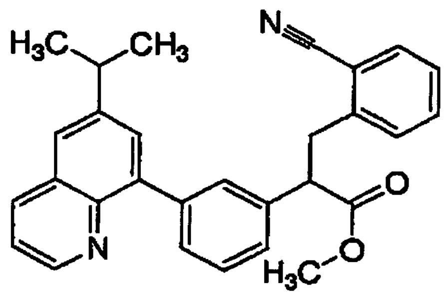


To a solution of **Example 83** (177mg, 0.37mmol) in diglyme (3mL) was added EDCI (93mg, 0.48mmol) and, after 10 min, N-hydroxyacetamidine (41mg, 0.55mmol). The resulting reaction mixture was stirred 3h at 110°C, then diluted with a saturated sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20 to 100:0) provided the title compound.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.30 (dd, 1H), 7.91 (dd, 2H), 7.77-7.74 (m, 3H), 7.59 (d, 1H), 7.56-7.53 (m, 2H), 7.47 (dd, 1H), 7.31 (t, 1H), 7.22 (d, 1H), 4.97 (t, 1H), 4.74 (dd, 1H), 3.48 (dd, 1H), 3.16 (q, 1H), 3.06 (s, 3H), 2.32 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H). LRMS (CI) 512 $(M+H)^+$.

EXAMPLE 85

3-(2-Cyano-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester

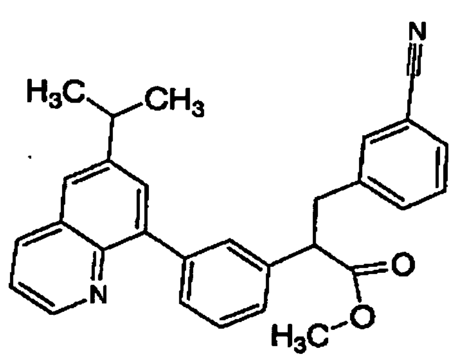


To a solution of **Quinoline 05** (100mg, 0.31mmol) in THF/DMF (1:1, 3mL) at -78°C was added potassium tert-butoxide (1M, 0.31mL, 0.31mmol) dropwise. The resulting reaction mixture was stirred 5min., then cannulated into a solution of 2-cyanobenzylbromide (123mg, 0.63mmol) in THF (1mL) at 21°C. After 3h, the reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20 to 20:80) provided the title compound.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.81 (dd, 1H), 8.28 (dd, 1H), 7.50 (s, 11H), 4.19 (t, 1H), 3.65 (dd, 1H), 3.61 (s, 3H), 3.39 (dd, 1H), 3.15 (m, 1H), 1.37 (d, 6H).

EXAMPLE 86

3-(3-Cyano-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester

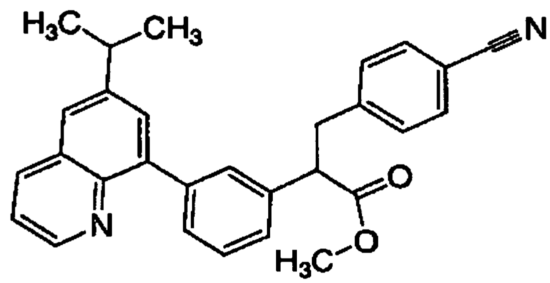


Following the procedures described above in **Example 85**, but substituting 3-cyanobenzylbromide for 2-cyanobenzylbromide, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.83 (dd, 1H), 8.29 (dd, 1H), 7.76 (d, 1H), 7.68 (s, 2H), 7.65-7.30(m, 8H), 4.10 (t, 1H), 3.60 (s, 3H), 3.49 (dd, 1H), 3.20 (dd, 1H), 3.15 (m, 1H), 1.39 (d, 6H).

EXAMPLE 87

3-(4-Cyano-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester

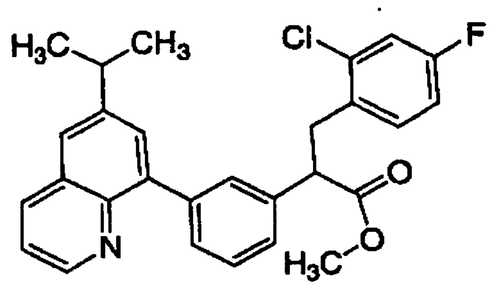


Following the procedures described above in **Example 85**, but substituting 4-cyanobenzylbromide for 2-cyanobenzylbromide, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 7.80 (d, 1H), 7.70-7.30(m, 10H), 4.10 (t, 1H), 3.61 (s, 3H), 3.52 (dd, 1H), 3.25 (dd, 1H), 3.18 (m, 1H), 1.38 (d, 6H).

EXAMPLE 88

3-(2-Chloro-4-fluoro-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester

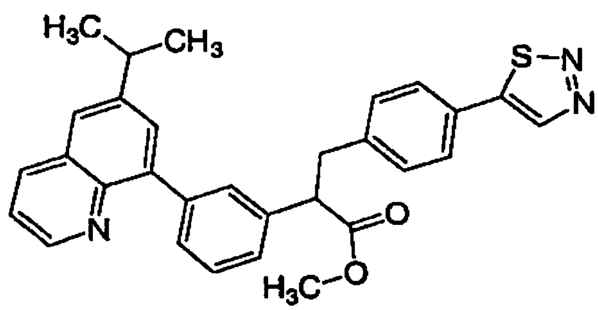


Following the procedures described above in **Example 85**, but substituting 2-chloro-4-fluorobenzyl bromide for 2-cyanobenzylbromide, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.83 (dd, 1H), 8.28 (dd, 1H), 7.77-7.30 (m, 9H), 6.98 (dt, 1H), 4.13 (t, 1H), 3.61 (s, 3H), 3.53 (dd, 1H), 3.25 (dd, 1H), 3.17 (m, 1H), 1.38 (d, 6H).

EXAMPLE 89

2-[3-(6-isopropylquinolin-8-yl)-phenyl]-3-[4-(1,2,3-thiadiazol-5-yl)-phenyl]-propionic acid methyl ester

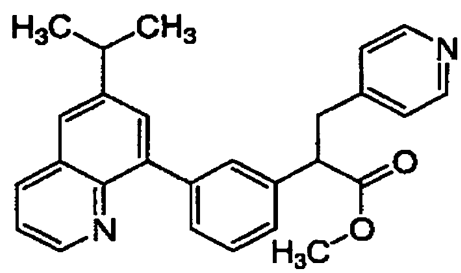


Following the procedures described above in **Example 85**, but substituting 4-(4-bromomethylphenyl)-[1,2,3]thiadiazole for 2-cyanobenzylbromide, the title compound was obtained.

^{1}H NMR (400MHz, acetone-*d6*): δ 9.29 (s, 1H), 8.82 (dd, 1H), 8.30 (dd, 1H), 8.06 (d, 2H), 7.76 (d, 1H), 7.65-7.59 (m, 3H), 7.49-7.23 (m, 5H), 4.11 (t, 1H), 3.61 (s, 3H), 3.52 (dd, 1H), 3.22 (dd, 1H), 3.09 (m, 1H), 1.31 (d, 6H).

EXAMPLE 90

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-pyridin-4-yl-propionic acid methyl ester

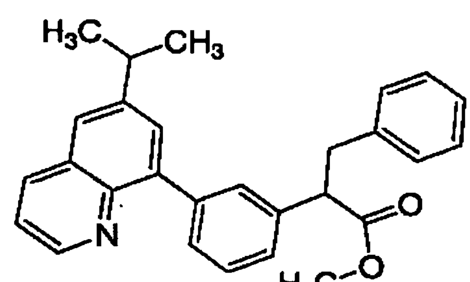


Following the procedures described above in **Example 85**, but substituting 4-picolyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.45 (d, 2H), 8.30 (dd, 1H), 7.80 (d, 1H), 7.70-7.35 (m, 6H), 7.25 (d, 2H), 4.15 (t, 1H), 3.60 (s, 3H), 3.46 (dd, 1H), 3.18 (m, 2H), 1.39 (d, 6H).

EXAMPLE 91

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-phenyl-propionic acid methyl ester

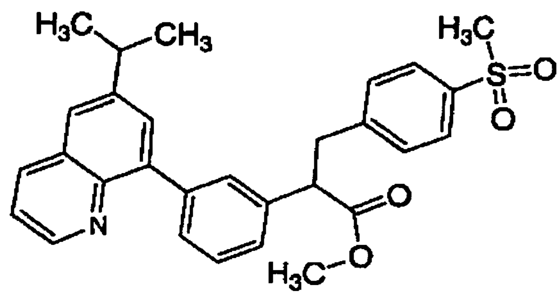


Following the procedures described above in **Example 85**, but substituting benzyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

[1]H NMR (300MHz, acetone-$d6$): δ 8.81 (dd, 1H), 8.30 (dd, 1H), 7.77 (d, 1H), 7.70-7.10 (m, 11H), 4.05 (t, 1H), 3.60 (s, 3H), 3.45 (dd, 1H), 3.18 (m, 1H), 3.12 (dd, 1H), 1.40 (d, 6H).

EXAMPLE 92

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionic acid methyl ester

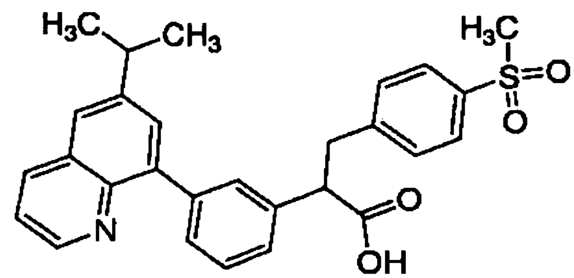


Following the procedures described above in **Example 85**, but substituting 4-methanesulfonylbenzyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

[1]H NMR (400MHz, acetone-$d6$): □8.85 (dd, 1H), 8.32 (dd, 1H), 7.81 (m, 3H), 7.72 (s, 1H), 7.69 (s, 1H), 7.61 (d, 1H), 7.56 (d, 2H), 7.49 (dd, 1H), 7.40 (t, 1H), 7.34 (d, 1H), 4.12 (t, 1H), 3.60 (s, 3H), 3.55 (dd, 1H), 3.38 (dd, 1H), 3.29 (m, 1H), 3.05 (s, 3H), 1.38 (d, 6H).

EXAMPLE 93

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionic acid

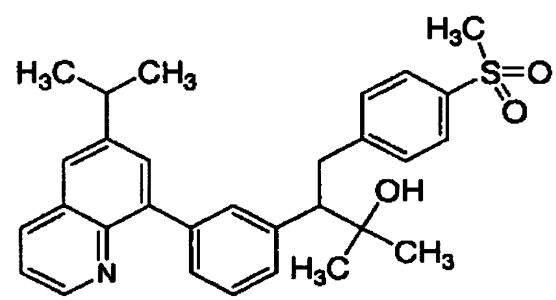


Following the procedures described above in **Example 8**, but substituting **Example 92** for **Example 7**, the title compound was obtained.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.85 (dd, 1H), 8.31 (dd, 1H), 7.82 (d, 2H), 7.78 (d, 2H), 7.68 (s, 1H), 7.60 (m, 3H), 7.48 (dd, 1H), 7.40 (m, 2H), 4.10 (t, 1H), 3.55 (dd, 1H), 3.25 (dd, 1H), 3.18 (m, 1H), 3.05 (s, 3H), 1.38 (s, 6H).

EXAMPLE 94

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-4-(4-methanesulfonyl-phenyl)-2-methyl-butan-2-ol



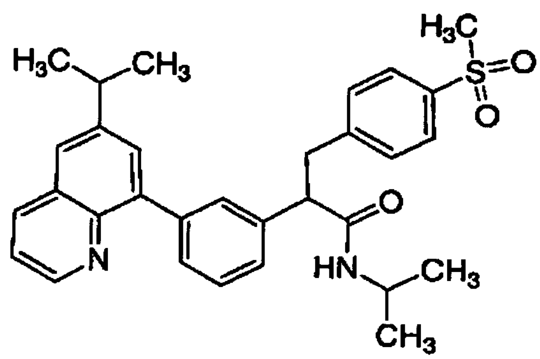
To a solution of **Example 92** (100mg, 0.2mmol) in CH_2Cl_2 (2mL) at -78°C was added methylmagnesium chloride (3M, THF, 0.2mL, 0.6mmol) dropwise. The resulting reaction mixture was stirred 1h at 21°C, then quenched with a saturated ammonium chloride solution. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 7:3) provided the title compound.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.85 (dd, 1H), 8.30 (dd, 1H), 7.80-7.65 (m, 5H), 7.55-7.45 (m, 4H), 7.35-7.20 (m, 2H), 3.70 (brs, 1H), 3.60 (dd, 1H),

3.30 (t, 1H), 3.15 (dd, 1H), 3.12 (m, 1H), 3.00 (s, 3H), 1.38 (d, 6H), 1.30 (s, 3H), 1.25 (s, 3H).

Example 95

N-Isopropyl-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionamide

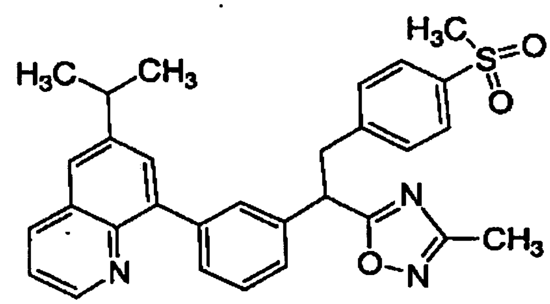


To a solution of **Example 93** (100mg, 0.21mmol) in CH_2Cl_2 (2mL) was added DMAP (26mg, 0.21mmol), EDCI (45mg, 0.23mmol), then isopropyl amine (1mL, 12mmol). The resulting reaction mixture was stirred 18h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20 to 20:80) provided the title compound.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.35 (dd, 1H), 7.95 (m, 1H), 7.85-7.75 (m, 4H), 7.65-7.52 (m, 3H), 7.50 (dd, 1H), 7.45-7.35 (m, 2H), 7.10 (brd, 1H), 3.88 (m, 2H), 3.59 (dd, 1H), 3.15 (m, 2H), 3.09 (s, 3H), 1.38 (d, 6H), 0.99 (d, 3H), 0.96 (d, 3H).

EXAMPLE 96

6-Isopropyl-8-{3-[2-(4-methanesulfonyl-phenyl)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl}-quinoline

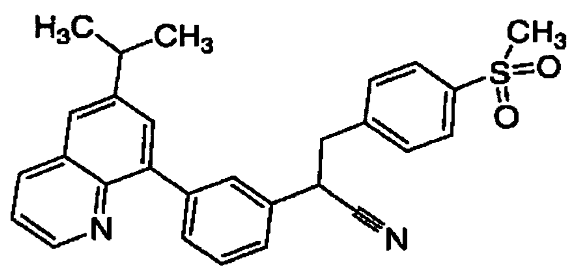


Following the procedures described above in **Example 84**, but substituting **Example 93** for **Example 83**, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 7.80 (m, 4H), 7.70-7.58 (m, 4H), 7.50 (dd, 1H), 7.40 (m, 2H), 4.85 (t, 1H), 3.78 (dd, 1H), 3.60 (dd, 1H), 3.28 (m, 1H), 3.05 (s, 3H), 2.30 (s, 3H), 1.40 (d, 6H).

EXAMPLE 97

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionitrile

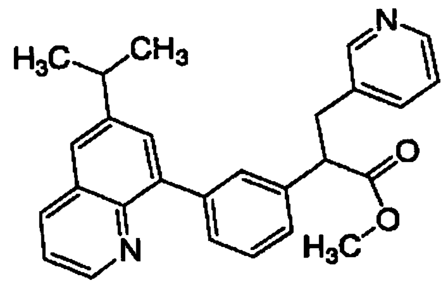


Following the procedures described above in **Example 85**, but substituting **Quinoline 07** for **Quinoline 05** and substituting 4-methanesulfonylbenzyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.85 (dd, 1H), 8.30 (dd, 1H), 7.90 (d, 2H), 7.80 (m, 2H), 7.70 (m, 2H), 7.60 (d, 2H), 7.45 (m, 3H), 4.57 (t, 1H), 3.45 (d, 2H), 3.19 (m, 1H), 3.09 (s, 3H), 1.40 (d, 6H).

EXAMPLE 98

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-pyridin-3-yl-propionic acid methyl ester

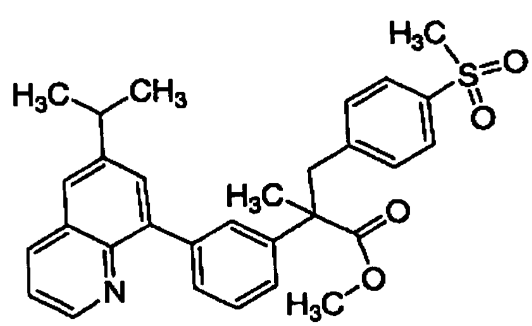


Following the procedures described above in **Example 85**, but substituting 3-picolyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.48 (d, 1H), 8.38 (dd, 1H), 8.29 (dd, 1H), 7.77 (d, 1H), 7.68 (t, 1H), 7.64 (m, 3H), 7.47 (dd, 1H), 7.41 (t, 1H), 7.34 (d, 1H), 7.22 (dd, 1H), 4.06 (t, 1H), 3.59 (s, 3H), 3.42 (dd, 1H), 3.16 (m, 2H), 1.37 (d, 6H).

EXAMPLE 99

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-2-methyl-propionic acid methyl ester

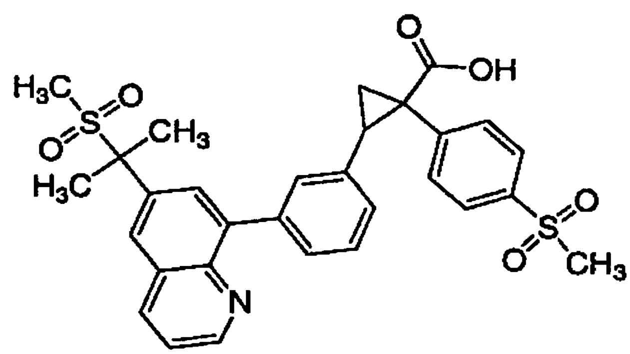


To a solution of **Example 92** (90mg, 0.185mmol) in THF/DMF (1:1, 2mL) at -78°C was added potassium tert-butoxide (1M, 0.19mL, 0.19mmol) dropwise followed by MeI (0,014mL, 0.22mmol) after 15 min. The resulting reaction mixture was stirred 18h at 21°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the title compound.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.84 (dd, 1H), 8.30 (dd, 1H), 7.80-7.70 (m, 5H), 7.62 (d, 1H), 7.49 (dd, 1H), 7.40 (m, 3H), 7.30 (d, 1H), 3.70 (s, 3H), 3.52 (dd, 2H), 3.20 (m, 1H), 3.03 (s, 3H), 1.55 (s, 3H), 1.40 (d, 6H).

EXAMPLE 100

2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid



Step 1: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-acrylic acid

Following the procedures described above in **Example 80, Step 1**, but substituting **Quinoline 03** for 3-bromobenzaldehyde, the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-acrylic acid compound was obtained as a white solid.

Step 2: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-acrylic acid methyl ester

Following the procedures described above in **Ester 01**, the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-acrylic acid methyl ester compound was obtained as a white solid.

Step 3: 2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid methyl ester

To a suspension of trimethylsulfoxonium iodide (400mg, 1.83mmol) in DMSO (25mL) at 0°C was added NaH (60%, 73mg, 1.83mmol). After 30min., 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-acrylic acid methyl ester from **Step 2** (688mg, 1.22mmol) was added and the resulting reaction mixture stirred for 18h at 21°C, then diluted with water and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 80:20) provided the 2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid methyl ester compound.

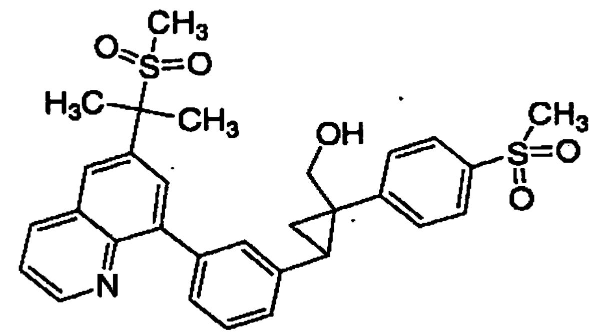
Step 4: 2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid

Following the procedures described above in **Example 08**, the 2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid compound was obtained as a white solid.

^{1}H NMR (400MHz, acetone-*d6*): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.13 (d, 1H), 7.92 (d, 2H), 7.85 (d, 2H), 7.80 (s, 1H), 7.66 (d, 1H), 7.55 (dd, 1H), 7.52 (d, 1H), 7.45 (m, 1H), 3.12 (s, 3H), 3.06 (t, 1H), 2.73 (s, 3H), 2.42 (dd, 1H), 1.98 (s, 6H), 1.74 (dd, 1H).

EXAMPLE 101

[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropyl]-methanol

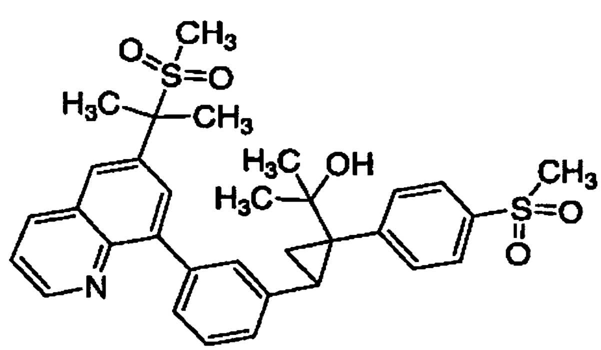


Using the compound from **Example 100, Step 3** as the starting material and following the procedures described above in **Example 15** and purification by flash chromatography (eluting with CH_2Cl_2/ethyl acetate, 60:40) provided the title compound.

^{1}H NMR (300MHz, acetone-*d6*) : δ 8.86 (dd, 1H), 8.45 (dd, 1H), 8.28 (d, 1H), 8.20 (d, 1H), 7.91 (brs, 1H), 7.87 (d, 2H), 7.80 (d, 2H), 7.55 (m, 2H), 7.48 (m, 2H), 3.95 (dd, 1H), 3.75 (dd, 1H), 3.55 (dd, 1H), 3.09 (s, 3H), 2.75 (m, 1H), 2.71 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.58 (dd, 1H), 1.46 (dd, 1H).

EXAMPLE 102

2-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropyl]-propan-2-ol

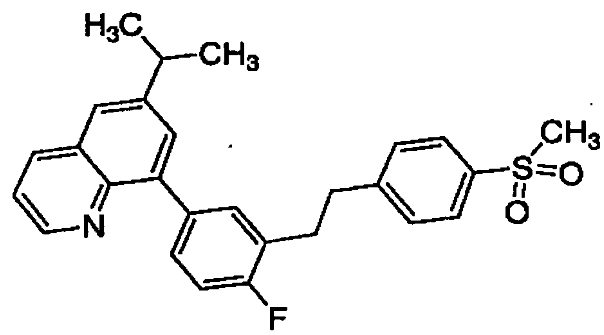


Using the compound from **Example 100, Step 3** as the starting material and following the procedures described above in **Example 29** and purification by flash chromatography (eluting with CH_2Cl_2/ethyl acetate, 60:40) provided the title compound.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.90 (dd, 1H), 8.45 (dd, 1H), 8.28 (d, 1H), 8.19 (d, 1H), 7.99 (s, 1H), 7.87 (s, 4H), 7.56 (m, 3H), 7.47 (t, 1H), 3.10 (s, 3H), 2.72 (s, 3H), 2.55 (t, 1H), 2.04 (m, 1H), 2.00 (s, 3H), 1.99 (s, 3H), 1.32 (dd, 1H), 1.17 (s, 3H), 1.06 (s, 3H).

EXAMPLE 103

8-{4-Fluoro-3-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline



Step 1: 4-Fluoro-3-hydroxymethyl-benzene-boronic acid

To a solution of 4-bromo-2-fluoro-benzyl alcohol (10g, 49mmol) in THF (500mL) at -78°C was added BuLi (2.5M, 43mL, 107mmol) dropwise keeping the internal temperature below -73°C. After 25 min., trimethylborate (25mL, 107mmol) was added and the resulting reaction mixture stirred for 15h at -78°C, 1h at 21°C, then diluted with HCl 10% and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. The residue was solidified from hexane/ethyl acetate with water (5 drops) to afford the 4-fluoro-3-hydroxymethyl-benzene-boronic acid compound as a white solid.

Step 2: [2-Fluoro-5-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol

Following the procedures described above in **Quinoline 01, Step 3**, and purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the [2-fluoro-5-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol compound.

Step 3: 2-Fluoro-5-(6-isopropyl-quinolin-8-yl)-benzaldehyde

A solution of [2-fluoro-5-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol from **Step 2** (2,23g, 7.55mmol) and MnO_2 (13g, 150mmol) in CH_2Cl_2 (70mL) was stirred at 21°C for 18h. The mixture was filtered through a pad of celite and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the 2-fluoro-5-(6-isopropyl-quinolin-8-yl)-benzaldehyde compound.

Step 4: 8-{4-Fluoro-3-[2-(4-methanesulfonyl-phenyl)-vinyl]-phenyl}-6-isopropyl-quinoline

A solution of 4-methanesulfonylbenzyl chloride (10g, 49mmol) and triphenylphosphine (12.8g, 49mmol) in acetonitrile (100mL) was stirred for 18h at reflux. The resulting reaction mixture was cooled to 21°C and the phosphorus salt crystallised from CH_3CN/ether. To a suspension of the salt (875mg, 1.87mmol) in THF (15mL) at 0°C was added potassium tert-butoxide (1M, THF, 1.87mL, 1.87mmol) dropwise and the resulting mixture stirred 30min at 0°C. The mixture was cooled to -78°C and the 2-fluoro-5-(6-isopropyl-quinolin-8-yl)-benzaldehyde from **Step 3** (0.5g, 1.7mmol, in THF) was added. After 90min. at 21°C, the reaction mixture was diluted with HCl 10% and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 60:40) provided the 8-{4-fluoro-3-[2-(4-methanesulfonyl-phenyl)-vinyl]-phenyl}-6-isopropyl-quinoline compound as a mixture of isomer (3:1).

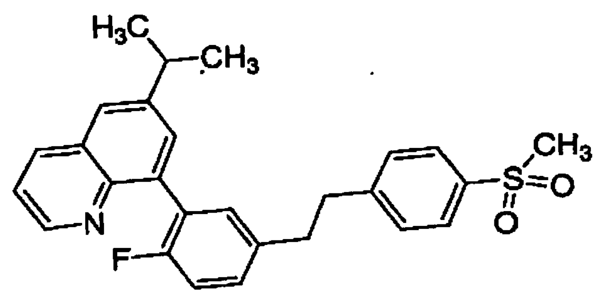
Step 5: 8-{4-Fluoro-3-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline

A solution of 8-{4-fluoro-3-[2-(4-methanesulfonyl-phenyl)-vinyl]-phenyl}-6-isopropyl-quinoline from **Step 4** (200mg, 0.45mmol) and polymer supported phenylsulfonyl hydrazide (1.0g) in toluene (10mL) was heated at 100°C for 18h. The resulting mixture was cooled at 21°C, filtered and the solvent evaporated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30 to 40:60) provided the 8-{4-fluoro-3-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline compound.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 7.87 (d, 2H), 7.78 (dd, 1H), 7.70-7.59 (m, 3H), 7.55 (d, 2H), 7.45 (dd, 1H), 7.17 (dd, 1H), 3.15 (m, 1H), 3.10 (brs, 4H), 3.05 (s, 3H), 1.40 (d, 6H).

EXAMPLE 104

8-{2-Fluoro-5-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline.

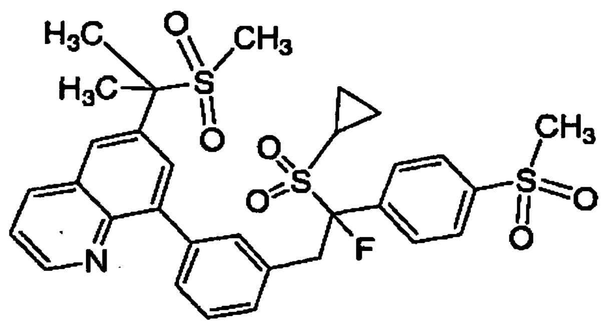


Following the procedures described above in **Example 103**, but substituting 3-bromo-4-fluorobenzyl alcohol for 4-bromo-2-fluoro-benzyl alcohol, the title compound was obtained.

^{1}H NMR (300MHz, acetone-*d6*): δ 8.78 (dd, 1H), 8.30 (dd, 1H), 7.83 (d, 2H), 7.81 (d, 1H), 7.63 (d, 1H), 7.51 (d, 2H), 7.45 (dd, 1H), 7.32 (m, 2H), 7.10 (dd, 1H), 3.15 (m, 1H), 3.10 (m, 4H), 3.04 (s, 3H), 1.37 (d, 6H).

EXAMPLE 105

8-{3-[2-Cyclopropanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

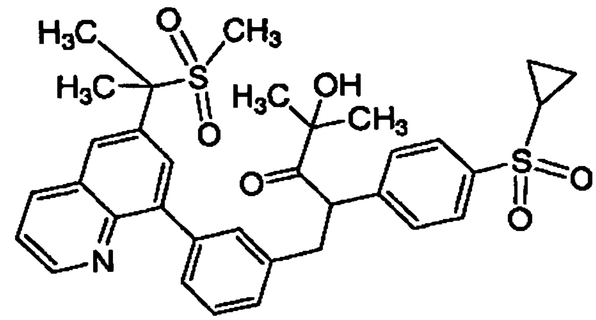


Following the procedures described above in **Example 1**, but substituting **Sulfone 03** for **Ketone 02** and then using the procedures described in **Example 37** (2 steps in a one pot reaction) followed by purification by flash chromatography (eluting with ethyl acetate/hexane) afforded the title compound as a pale beige powder. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH/i-PrOH/MeOH, 30:30:30:10, retention time 8.1 and 10.2 min) to give **Examples 105A** and **Example 105B**.

^{1}H NMR (400MHz, ace-*d6*): δ 8.88 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.01-7.94 (m, 5H), 7.57-7.53 (s, 3H), 7.30 (t, 1H), 7.24 (d, 1H), 4.05-3.97 (m, 2H), 3.08 (s, 3H), 2.70 (s, 3H), 2.49-2.43 (m, 1H), 1.97 (s, 3H), 1.96 (s, 3H), 1.18-1.08 (m, 2H), 1.00-0.93 (m, 1H), 0.84-0.77 (m, 1H).

EXAMPLE 106

2-(4-Cyclopropanesulfonyl-phenyl)-4-hydroxy-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-methyl-pentan-3-one

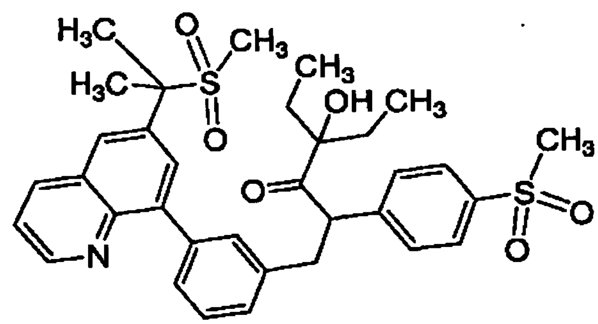


Example 106 was prepared by following the procedures described above in **Example 1**, but substituting **Sulfone 09** for **Ketone 02**. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:1 to 8:2) afforded the title compound.

^{1}H NMR (400MHz, ace-*d6*): δ 8.93 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.05 (d, 1H), 7.83 (d, 2H), 7.67 (d, 2H), 7.58-7.54 (m, 2H), 7.51 (app d, 1H), 7.33 (t, 1H), 7.22 (app d, 1H), 5.18 (d, 1H), 4.48 (s, 1H), 3.45 (dd, 1H), 3.07 (dd, 1H), 2.71 (s, 3H), 2.60 (m, 1H), 1.95 (s, 6H), 1.14 (dd, 2H), 1.10 (s, 3H), 1.05 (s, 3H), 1.00 (m, 2H).

EXAMPLE 107

4-Ethyl-4-hydroxy-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-hexan-3-one



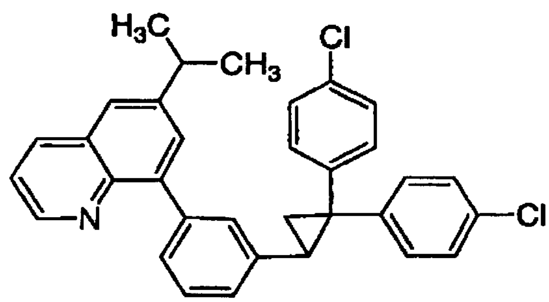
Example 107 was prepared by following the procedures described above in **Example 1**, but substituting **Ketone 12** for **Ketone 02**. Purification by flash

chromatography (eluting with ethyl acetate/hexane, 3:2) afforded the title compound as a white foam.

^1H NMR (400MHz, acetone-*d6*): δ 9.93 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.85 (m, 2H), 7.67 (m, 2H), 7.57 (m, 2H), 7.48 (dd, 1H), 7.32 (t, 1H), 7.20 (dd, 1H), 5.13 (t, 1H), 4.15 (s, OH), 3.42 (dd, 1H), 3.09 (dd, 1H), 3.03 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H), 1.6-1.4 (m, 4H), 0.49 (t, 6H).

EXAMPLE 108

8-{3-[2,2-Bis-(4-chloro-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline



Step 1: [Bis-(4-chloro-phenyl)-methylene]-hydrazine

A solution of bis-(4-chloro-phenyl)-methanone (5.0g, 19.9mmol) and hydrazine monohydrate (5mL, 103mmol) in ethanol (25mL) was heated to reflux 18h, cooled to 21°C, and filtered to afforded the [bis-(4-chloro-phenyl)-methylene]-hydrazine compound as a yellow solid.

Step 2: Diazo bis-(4-chloro-phenyl)-methane

To a solution of [bis-(4-chloro-phenyl)-methylene]-hydrazine from Step 1 (2.0g, 7.5mmol) in $CHCl_3$ (20mL) was added MnO_2 (5.0g, 57mmol). The resulting reaction mixture was stirred 1h at 21°C, then filtered on a bed of $MgSO_4$ and the filtrate concentrated to provided the diazo bis-(4-chloro-phenyl)-methane compound as a purple solid.

Step 3: 6-Isopropyl-8-(3-vinyl-phenyl)-quinoline

To a solution of methyl triphenylphosphonium bromide (5.2g, 14.6mmol) in THF (20mL) at 0°C was added potassium tert-butoxide (1M, THF, 14.5mL, 14.5mmol) followed, after 15 min, by **Quinoline 04** (3.33g, 12.1mmol) in THF (5mL). The resulting reaction mixture was stirred 2h at 0°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 90:10) provided the 6-isopropyl-8-(3-vinyl-phenyl)-quinoline compound.

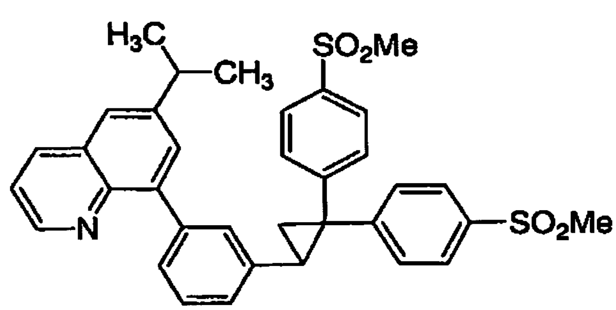
Step 4: 8-{3-[2,2-Bis-(4-chloro-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline

A solution of the 6-isopropyl-8-(3-vinyl-phenyl)-quinoline from **Step 3** (230mg, 0.84mmol) and the diazo bis-(4-chloro-phenyl)-methane from **Step 2** (530mg, 2.0mmol) in benzene (10mL) was heated to reflux for 18h, cooled to 21°C, and purified by flash chromatography (eluting with hexane/ethyl acetate, 90:10) to provide the 8-{3-[2,2-bis-(4-chloro-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline compound as a yellow foam.

^{1}H NMR (400MHz, acetone-d_6): δ 8.79 (dd, 1H), 8.28 (dd, 1H), 7.73 (d, 1H), 7.47-7.39 (m, 4H), 7.33-7.21 (m, 8H), 7.14 (m, 2H), 3.13 (m, 1H), 3.03 (dd, 1H), 2.18 (dd, 1H), 1.80 (dd, 1H), 1.36 (d, 6H).

EXAMPLE 109

8-{3-[2,2-Bis-(4-methanesulfonyl-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline



Step1: Bis-(4-methylsulfanyl-phenyl)-methanol

To a solution of 4-bromothioanisole (1.06g, 5.2mmol) in THF (20mL) at -78°C was added BuLi (2.3M, hexane, 2.2mL, 5mmol) dropwise. After 30min at -78°C, 4-methylthiobenzaldehyde (685mg, 4.5mmol) was added. After 20 min., the resulting reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20) provided the bis-(4-methylsulfanyl-phenyl)-methanol compound.

Step 2: Bis-(4-methylsulfanyl-phenyl)-methanone

A solution of bis-(4-methylsulfanyl-phenyl)-methanol from **Step 1** (1.0g, 3.6mmol) and MnO_2 (3g, 35mmol) in CH_2Cl_2 (30mL) was stirred at 21°C for 18h. The resulting mixture was filtered through a pad of celite and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 85:15) provided the bis-(4-methylsulfanyl-phenyl)-methanone compound.

Step 3: Bis-(4-methanesulfonyl-phenyl)-methanone

A solution of bis-(4-methylsulfanyl-phenyl)-methanone from **Step 2** (0.9g, 3.2mmol), NMO (2.2g, 19mmol) and OsO_4 (4%, H_2O, 1mL, 0.16mmol) in acetone (20mL) was stirred 18h at 21°C. The resulting reaction mixture was diluted with a sodium metabisulfite solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the bis-(4-methanesulfonyl-phenyl)-methanone compound.

Step 4: 8-{3-[2,2-Bis-(4-methanesulfonyl-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline

The procedures described above in **Example 108** were followed, but substituting bis-(4-methanesulfonyl-phenyl)-methanone from **Step 3** instead of bis-(4-chloro-phenyl)-methanone. Purification by flash chromatography (eluting with ethyl

acetate/hexane, 3:7) afforded the 8-{3-[2,2-bis-(4-methanesulfonyl-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline compound as a white solid.

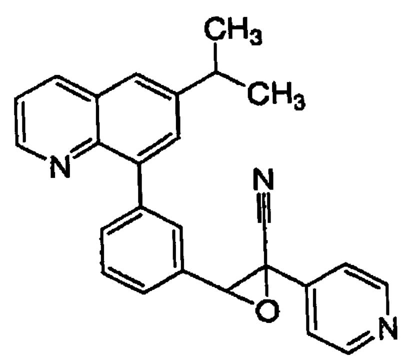
^{1}H NMR (400MHz, acetone-d_6): δ 8.81 (dd, 1H), 8.29 (dd, 1H), 7.88 (d, 2H), 7.76-7.70 (m, 5H), 7.58 (d, 2H), 7.48-7.40 (m, 4H), 7.21 (t, 1H), 7.05 (d, 1H), 3.23 (dd, 1H), 3.14 (m, 1H), 3.09 (s, 3H), 2.93 (s, 3H), 2.4 (dd, 1H), 1.97 (dd, 1H), 1.35 (d, 6H).

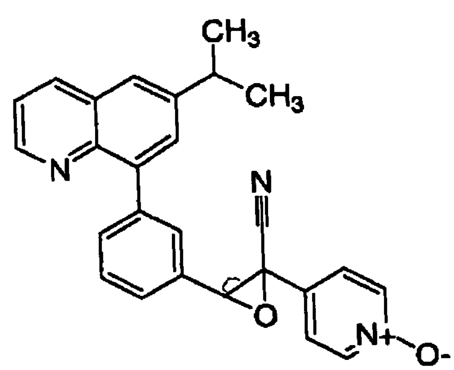
EXAMPLES 110 and 111

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-oxirane-2-carbonitrile

and

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-4-yl)-oxirane-2-carbonitrile





Step 1: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-acrylonitrile

Following the procedures described above in **Example 78, Step 2**, but substituting 4-methanesulfonylacetonitrile for 4-pyridinylacetonitrile, and purification by flash chromatography (eluting with ethyl acetate/hexane, 3:7) afforded the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-acrylonitrile compound.

Step 2: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-oxirane-2-carbonitrile

To a solution of 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-acrylonitrile from **Step 1** (75mg, 0.3mmol) in CH_2Cl_2/MeOH (1:1, 2mL) was added MMPP (148mg, 0.3mmol). The resulting reaction mixture was stirred 18h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with EtOH/ethyl acetate, 10:90) provided the title compounds.

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-oxirane-2-carbonitrile: ^{1}H NMR (500MHz, acetone-d_6): δ 8.83 (dd, 1H), 8.74 (m, 2H), 8.32 (dd, 1H), 7.95 (d, 1H), 7.90 (m, 1H), 7.81 (d, 1H), 7.79 (d, 1H), 7.61 (m, 2H), 7.56 (dd, 2H), 7.49 (dd, 1H), 4.7 (s, 1H), 3.18 (m, 1H), 1.38 (d, 3H), 1.37 (d, 3H).

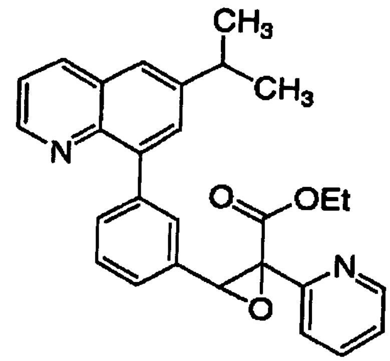
3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-4-yl)-oxirane-2-carbonitrile: ^{1}H NMR (500MHz, acetone-d_6): δ 8.83 (dd, 1H), 8.33 (dd, 1H), 8.27 (m, 2H), 7.92 (s, 1H), 7.90 (m, 1H), 7.81 (d, 1H), 7.78 (d, 1H), 7.61-7.56 (m, 4H), 7.50 (dd, 1H), 4.8 (s, 1H), 3.18 (m, 1H), 1.39 (d, 3H), 1.37 (d, 3H).

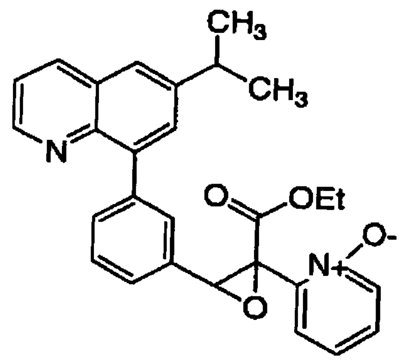
EXAMPLES 112 and 113

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-2-yl-oxirane-2-carboxylic acid ethyl ester

and

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-2-yl)-oxirane-2-carboxylic acid ethyl ester





Following the procedures described in **Example 110**, but substituting 4-pyridinylacetonitrile for ethyl 2-pyridinylacetate, and purification by flash chromatography (eluting with EtOH/ethyl acetate, 10:90) provided the title compounds.

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-2-yl-oxirane-2-carboxylic acid ethyl ester: ^{1}H NMR (500MHz, acetone-d_6): δ 8.80 (dd, 1H), 8.29 (dd, 1H), 8.05 (d, 1H), 7.76 (d, 1H), 7.61 (m, 1H), 7.57 (s, 1H), 7.53 (dd, 1H), 7.50 (d, 1H), 7.46 (dd, 1H), 7.35-7.27 (m, 5H), 5.11 (s, 1H), 4.20 (m, 2H), 3.16 (m, 1H), 1.37 (d, 6H), 1.20 (t, 3H).

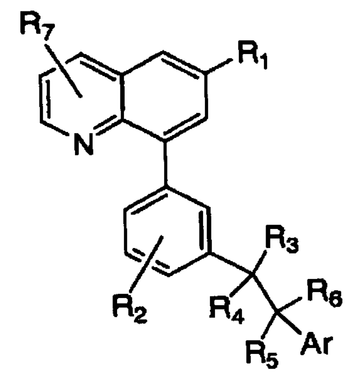
3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-2-yl)-oxirane-2-carboxylic acid ethyl ester: ^{1}H NMR (500MHz, acetone-d_6): δ 8.83 (dd, 1H), 8.59 (d, 1H), 8.31 (dd, 1H), 7.89 (m, 1H), 7.87 (m, 2H), 7.75 (m, 2H), 7.48 (m,

3H), 7.42 (m, 1H), 4.9 (s, 1H), 4.05 (m, 2H), 3.18 (m, 1H), 1.39 (d, 3H), 1.37 (d, 3H), 0.89 (t, 3H).

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

WHAT IS CLAIMED IS:

1. A compound represented by (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, pyridinone, pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-5 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3;

R_1 is hydrogen, halogen; or a –C_{1-6}alkyl, –cycloC_{3-6}alkyl, -C_{1-6}alkenyl, –C_{0-4}alkyl–C(O)–C_{0-4}alkyl, –C_{1-6}alkoxy, aryl, heteroaryl, –CN, -heterocycloC_{3-6}alkyl, –amino, –C_{1-6}alkylamino, –(C_{1-6}alkyl)(C_{1-6}alkyl)amino, -C_{1-6}alkyl(oxy)C_{1-6}alkyl, –C(O)NH(aryl), –C(O)NH(heteroaryl), –SO_nNH(aryl), -SO_nNH(heteroaryl), –SO_nNH(C_{1-6}alkyl), –C(O)N(C_{0-6}alkyl)(C_{0-6}alkyl), -NH-SO_n–(C_{1-6}alkyl), –carbamoyl, –(C_{1-6}alkyl)–O–C(CN)–dialkylamino, or –(C_{0-6}alkyl)–SO_n–(C_{1-6}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, –OH, -CN, –C_1-C_6alkyl, –C(O)(heterocycloC_{3-6}alkyl), –C(O)–O–(C_{0-6}alkyl), –C(O)–O–aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, –cycloC_{3-6}alkyl, heterocycloC_{3-6}alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or –SO_n–(C_{1-6}alkyl);

R_2, R_3, R_6, and R_7 are each independently hydrogen, halogen, hydroxyl, –C_{1-6}alkyl, or –C_{1-6}alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or OH;

R4 is hydrogen, halogen, –CN, phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl, wherein the phenyl, oxadiazolyl, or –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen, CN, CF3,–SO_n–C_{1-6}alkyl, or C_{1-6}alkyl substituents, and the alkyl group is optionally substituted with OH

R5 is hydrogen, hydroxyl, –CN; or a –C_{1-6}alkyl, –C(O)C_{1-6}alkyl, -C(O)-aryl, –C(O)–pyridyl, –C(O)–O–C_{0-6}alkyl, –C(O)–C_{3-7}cycloalkyl, –C_{1-6}alkyl–C_{3-7}cycloalkyl, –C_{1-6}alkyl(C_{3-7}cycloalkyl)$_2$, –C_{1-6}alkyl-aryl, –C(O)–N(C_{0-6}alkyl)$_2$, –SO_naryl, –SO_n–C_{1-6}alkyl, –SO_n–C_{3-7}cycloalkyl, –SO_n–N(C_{0-6}alkyl)$_2$, -P(O)(C_{1-6}alkyl)$_2$, –P(O)(C_{1-6}alkoxy)$_2$, phenyl, pyridyl, –SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, –CN, -CF_3, –C_{1-6}alkyl, –SO_n–C_{1-6}alkyl, –C(O)–O–C_{0-6}alkyl, or hydroxyC_{1-6}alkyl substituents;

or R_5 and R_6 form =O;

or R_6 and R_3 form –CH_2– or –O–; and

n is 0, 1, or 2.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar is phenyl optionally substituted with 1-5 independent -C_{1-6}alkyl, -OH, -CN, halogen, -CF_3, -(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl), -(C_{0-6}alkyl)-SO_n-NH-(C_{1-6}alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C_{1-6}alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF_3.

3. The compound according to Claim 2, or a pharmaceutically acceptable salt thereof, wherein R_4 is hydrogen, halogen, –CN, or –C(O)–O–C_{0-6}alkyl, wherein the –C(O)–O–C_{0-6}alkyl is optionally substituted with 1-3 independent halogen or C_{1-4}alkyl substituents.

4. The compound according to Claim 2, or a pharmaceutically acceptable salt thereof, wherein R_4 is oxadiazolyl optionally substituted with 1-3 independent halogen or C_{1-4}alkyl substituents.

5. The compound according to Claim 2, or a pharmaceutically acceptable salt thereof, wherein R_6 and R_3 form $-CH_2-$.

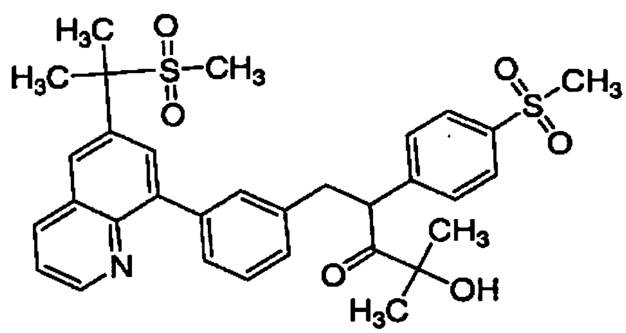
6. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridyl or pyridyl *N*-oxide.

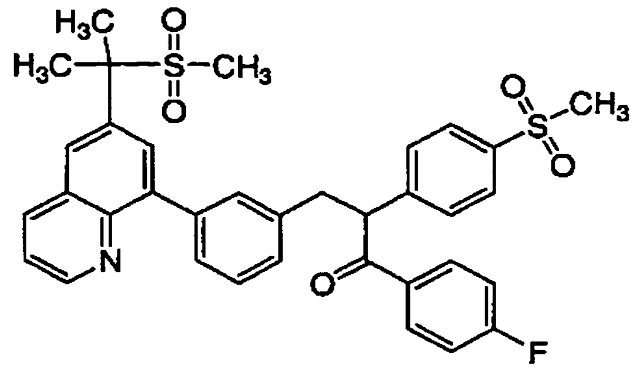
7. The compound according to Claim 6, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl optionally substituted with 1-3 independent halogen or C_{1-4}alkyl substituents.

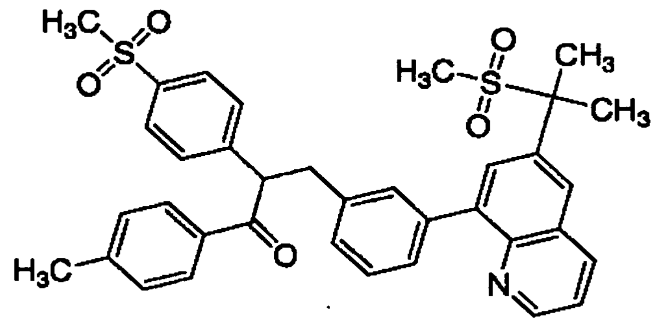
8. The compound according to Claim 6, or a pharmaceutically acceptable salt thereof, wherein R_4 is hydrogen, halogen, $-CN$, or $-C(O)-O-C_{0-6}$alkyl, wherein the $-C(O)-O-C_{0-6}$alkyl is optionally substituted with 1-3 independent halogen or C_{1-4}alkyl substituents.

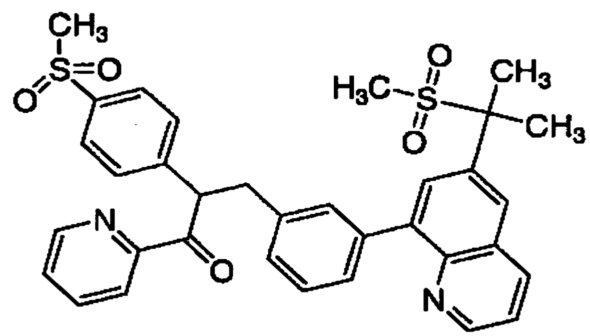
9. The compound according to Claim 6, or a pharmaceutically acceptable salt thereof, wherein R_6 and R_3 form $-O-$.

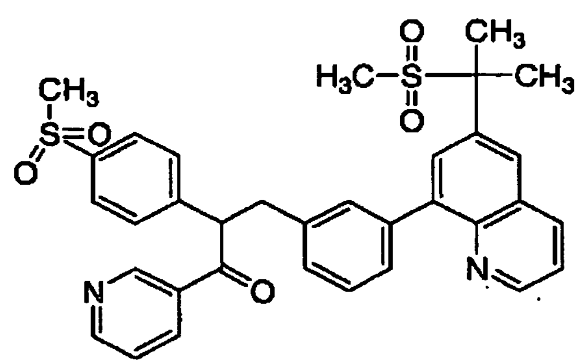
10. The compound according to Claim 1, represented by

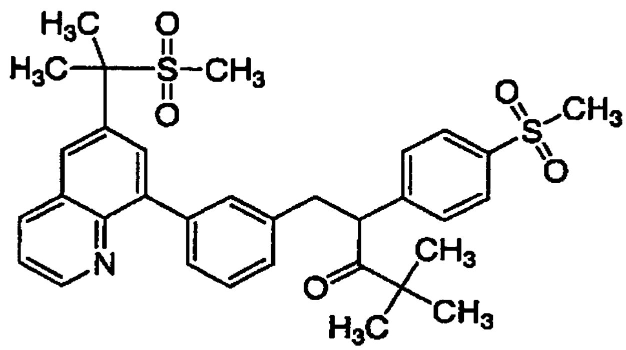








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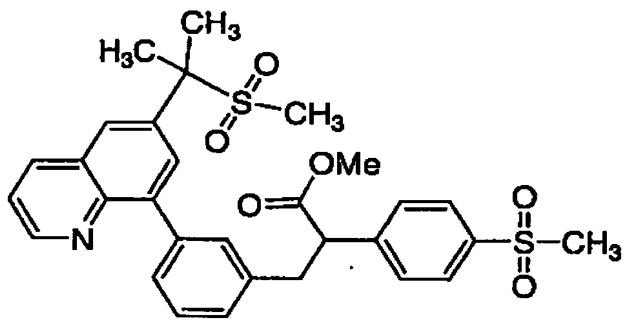
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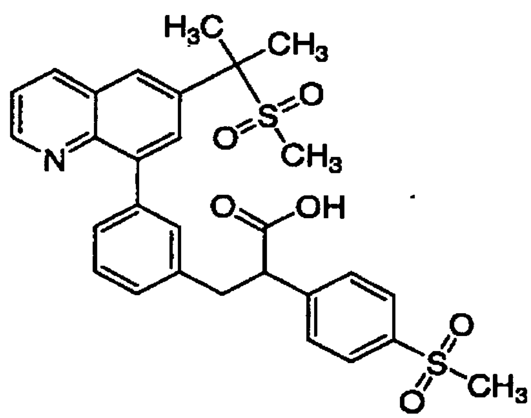
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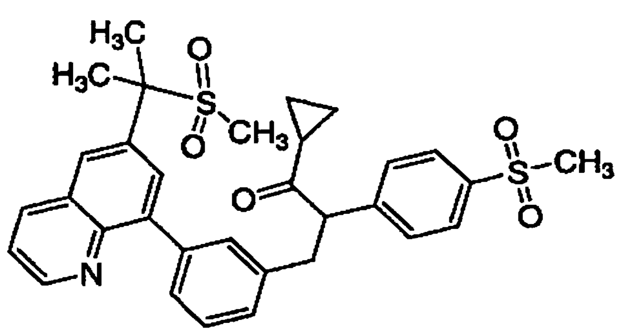
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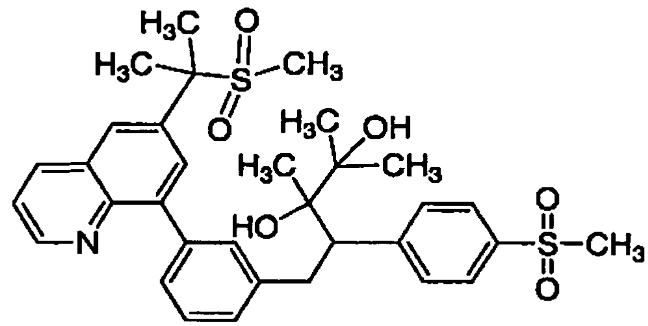

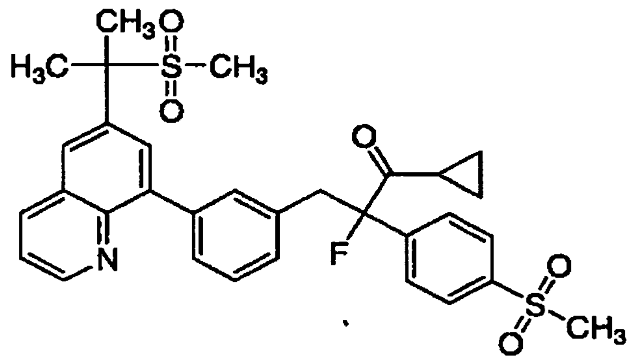

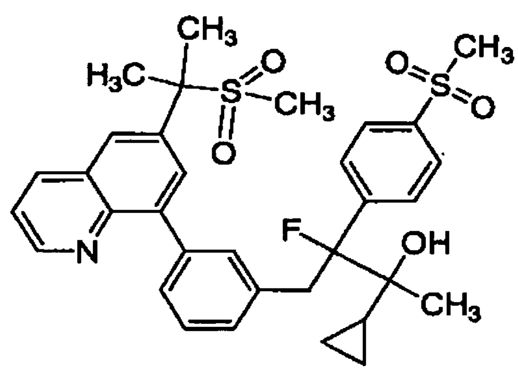

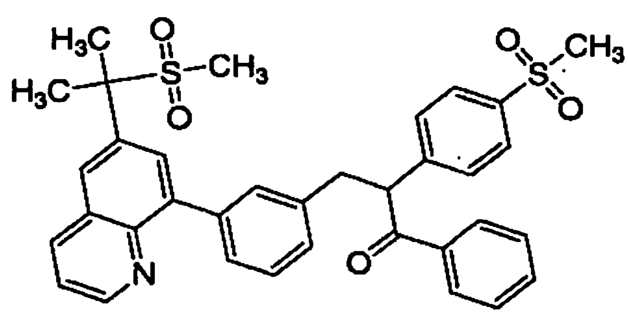

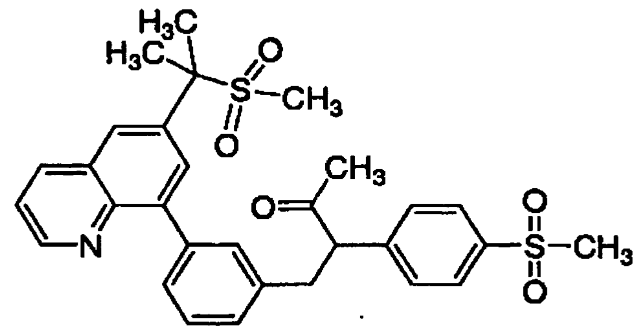
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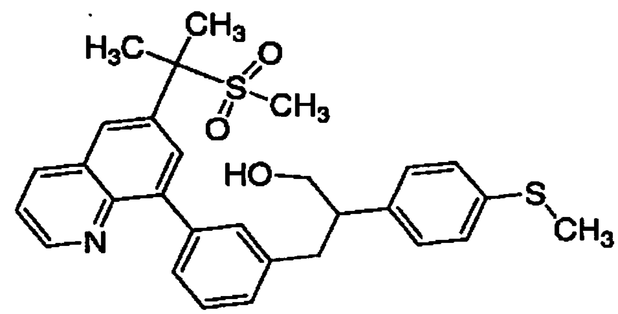
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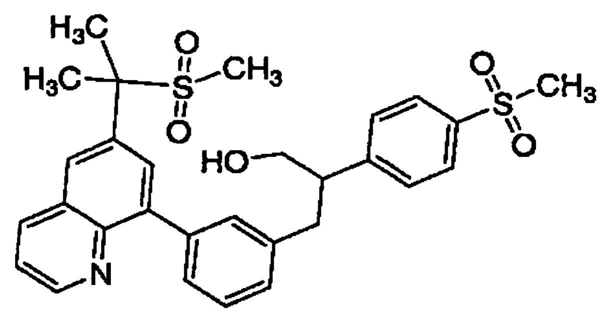
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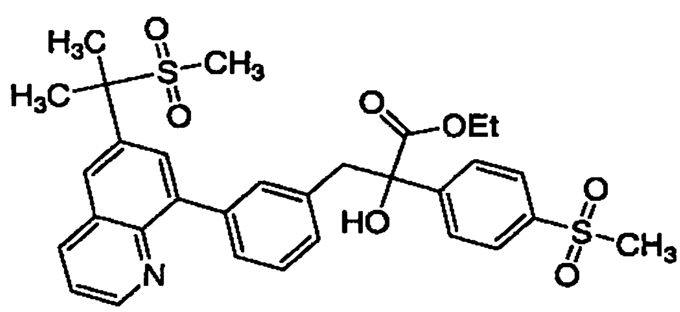
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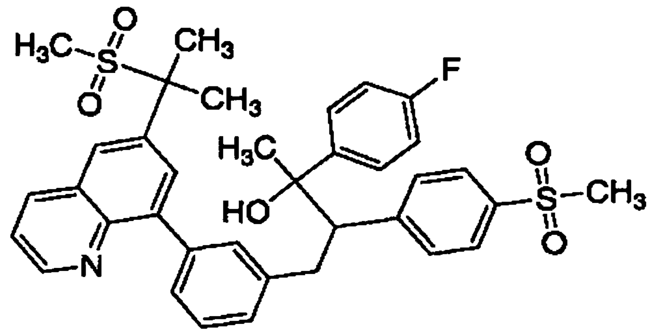
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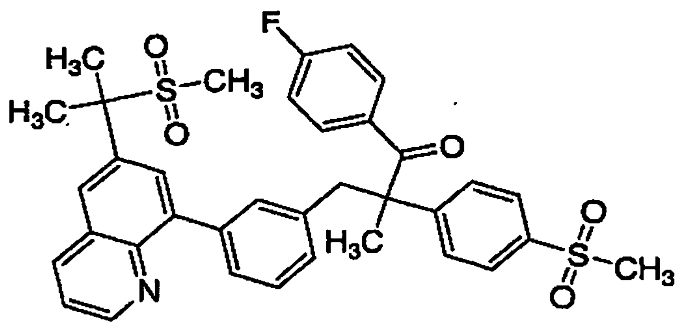
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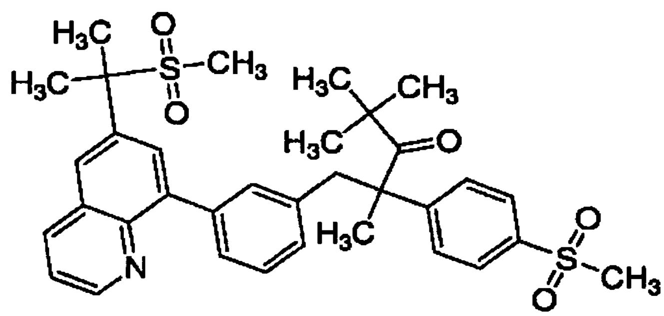
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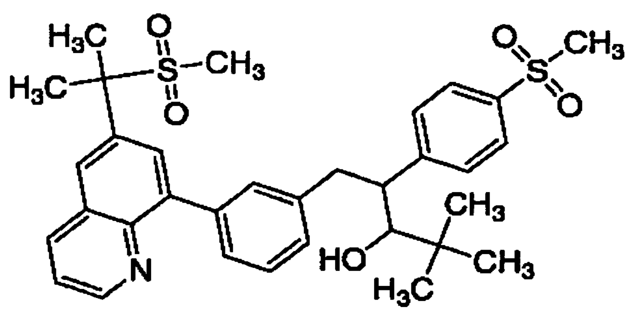
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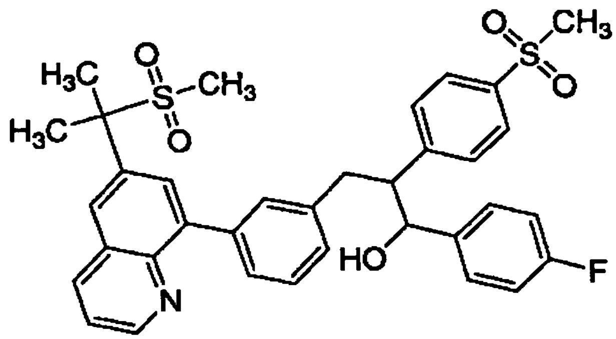

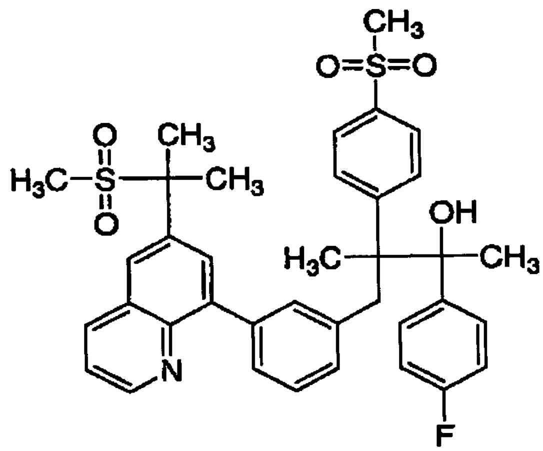

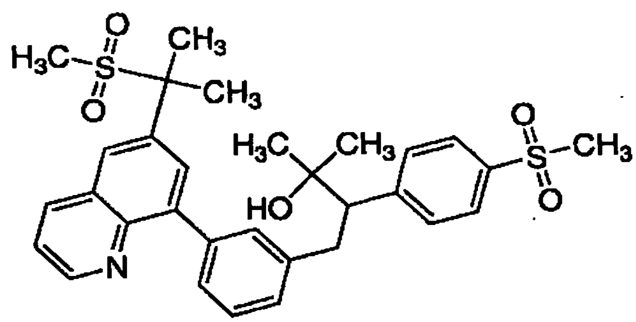

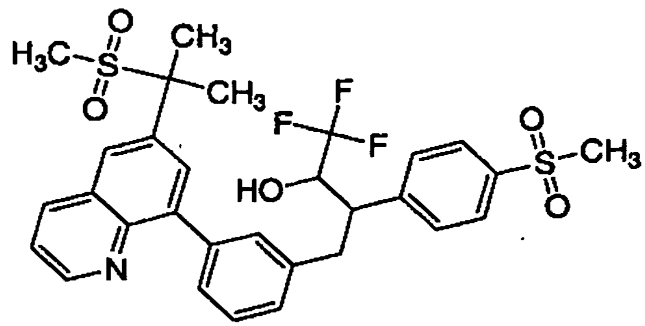
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CH3
CH3
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F
F
HO
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S
CH3
O
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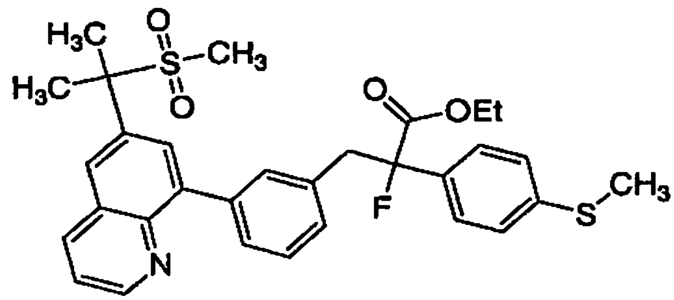
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CH3
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CH3
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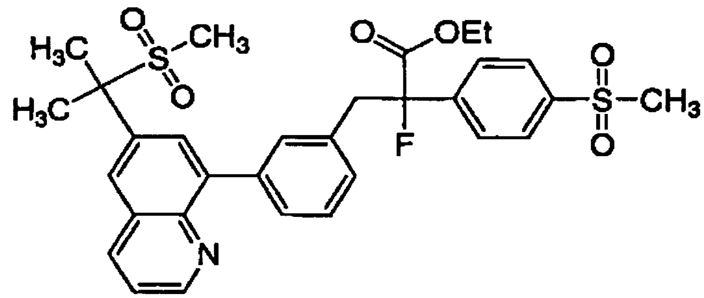
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CH3
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OEt
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CH3
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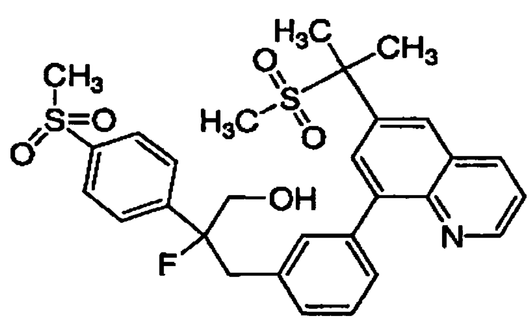
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CH3
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H3C
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OH
F
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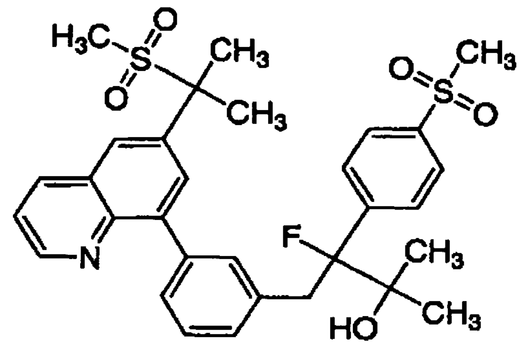
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O
O
CH3
CH3
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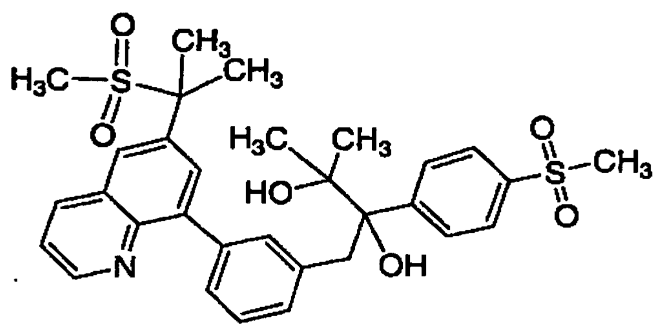
S
CH3
O
N
F
CH3
HO
CH3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H3C
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CH3
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H3C
CH3
O
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CH3
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HO
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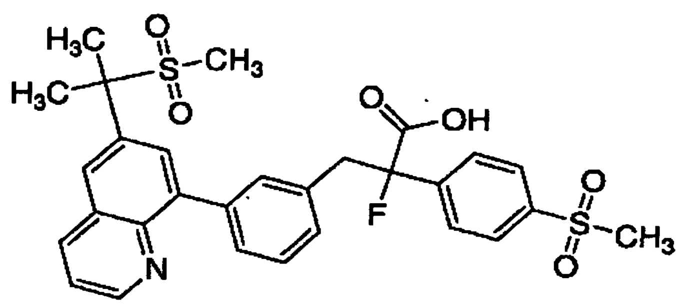
OH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H3C
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OH
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CH3
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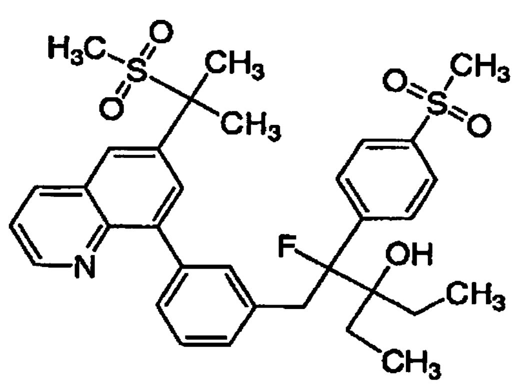
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CH3
CH3
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CH3
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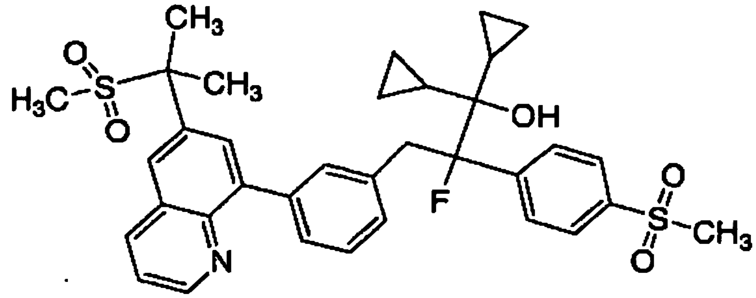
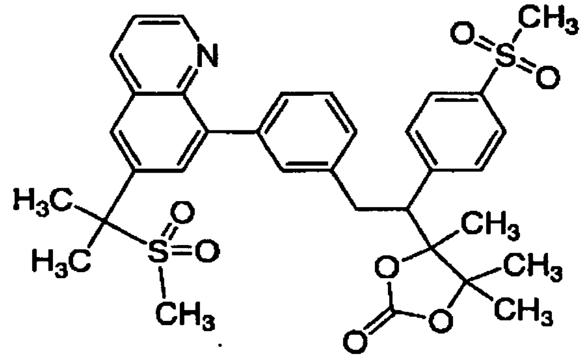
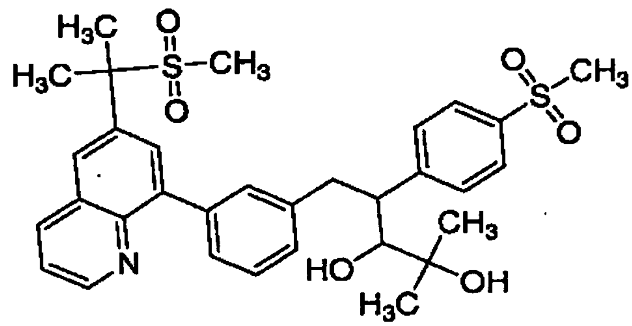
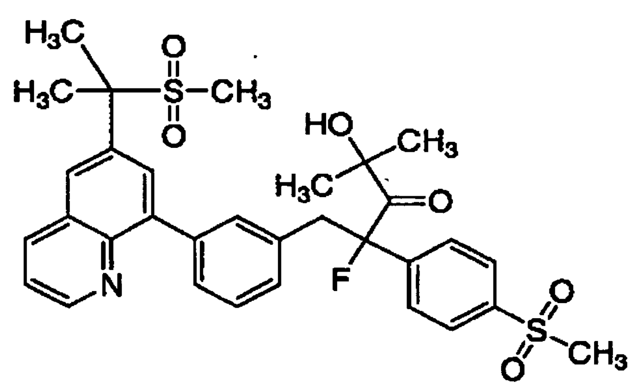
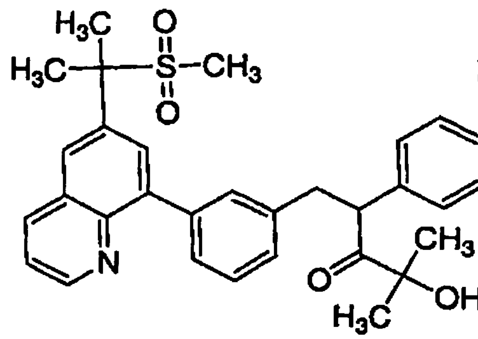
F
OH
CH3
CH3

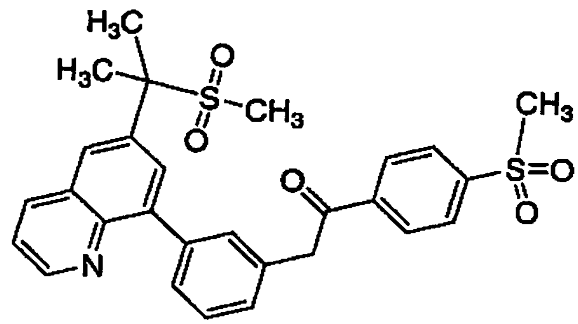


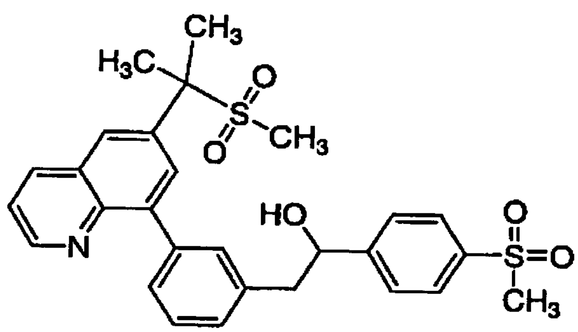


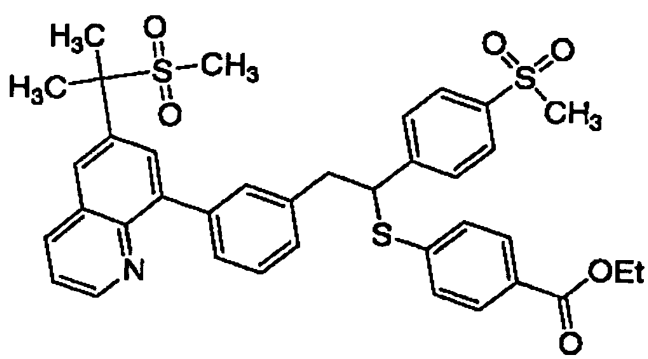


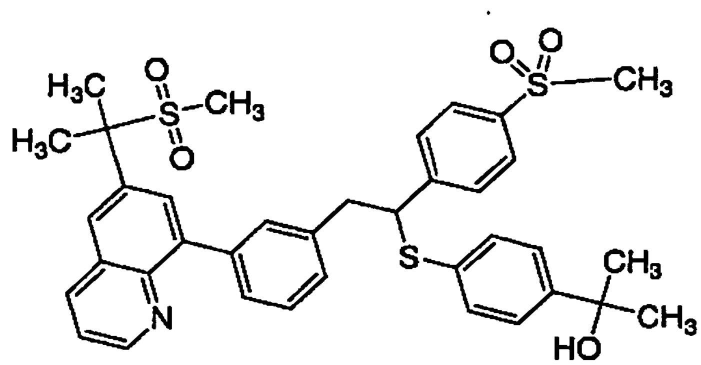


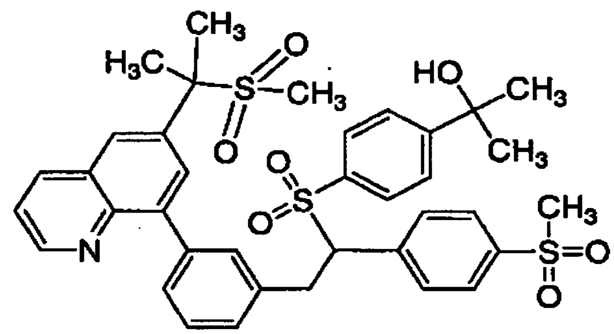


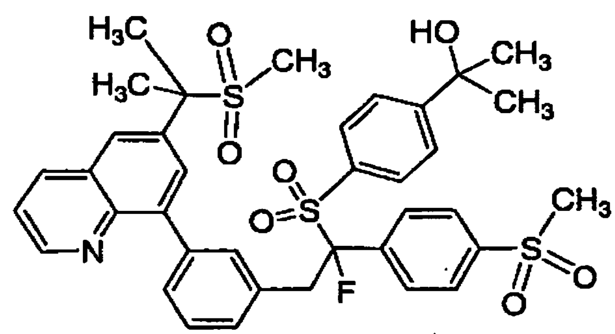


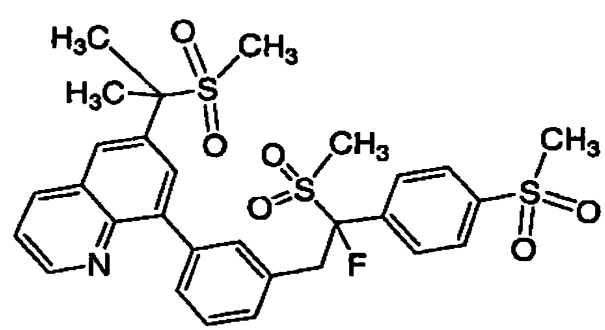


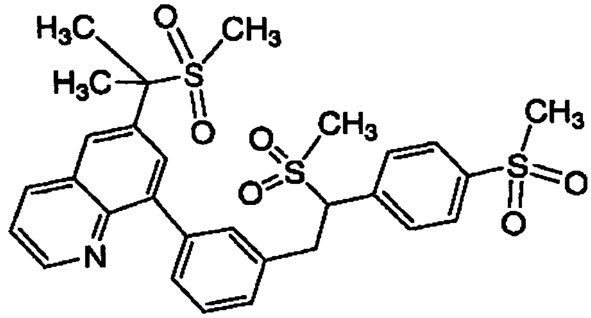








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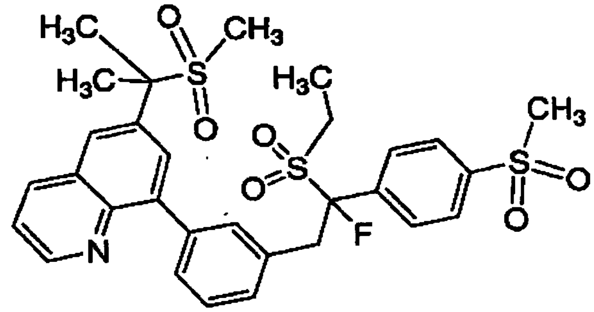
CH3
H3C
S
O
CH3
O
S
CH3
O
S
O
O
N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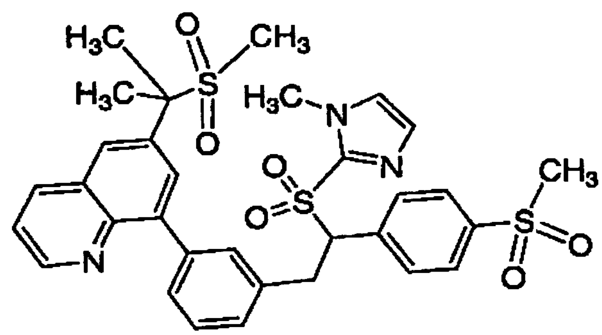
O
CH3
H3C
S
H3C
O
CH3
O
S
S
O
O
O
F
N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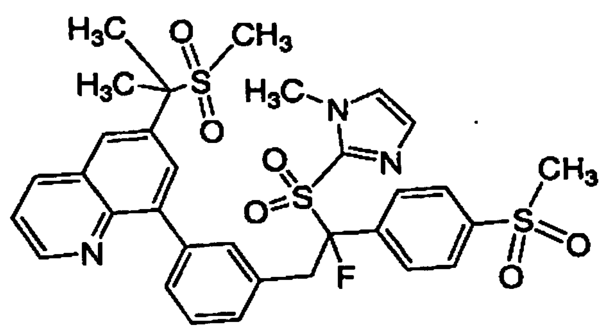
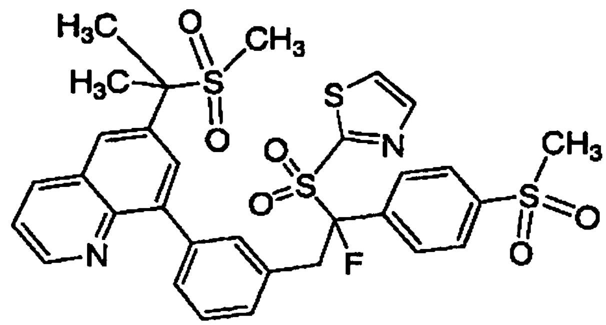
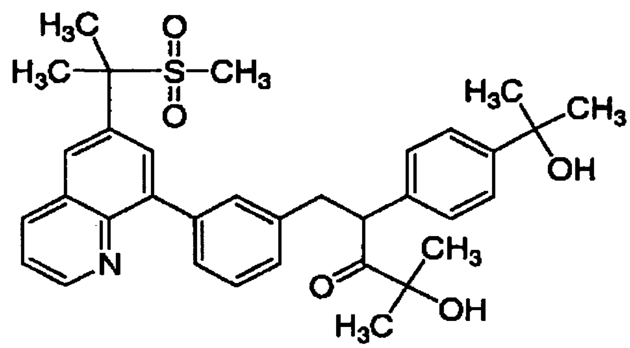
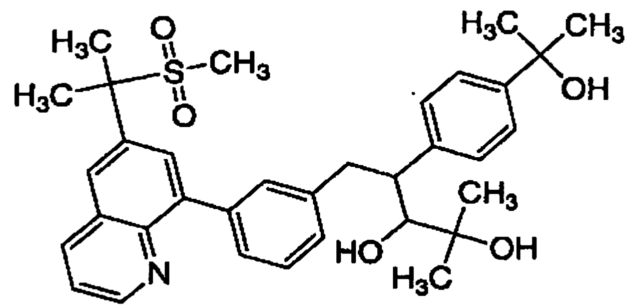
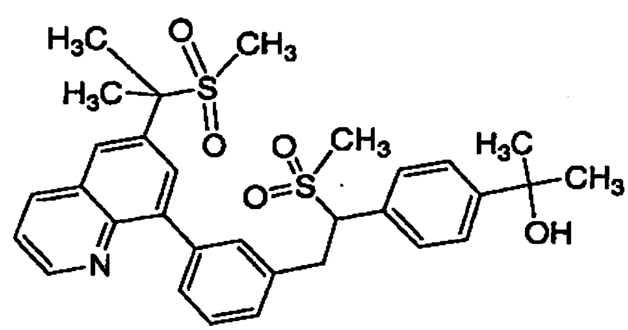
CH3
H3C
S
H3C
N
O
O
N
CH3
S
O
S
O
O
N

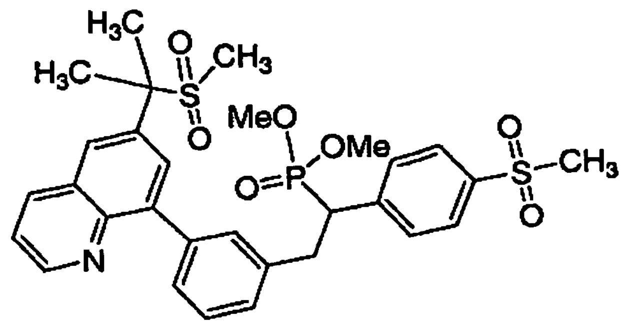

H3C
O
CH3
H3C
S
H3C
N
O
O
N
CH3
S
O
S
O
O
F
N

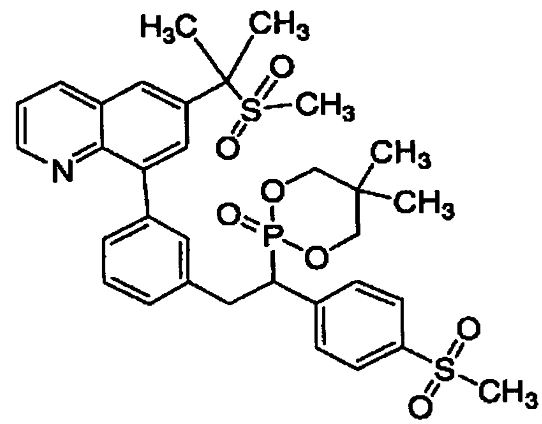


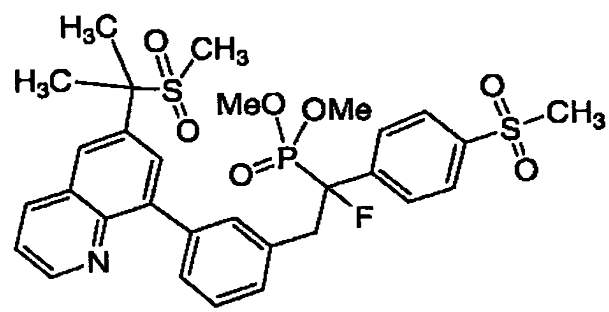


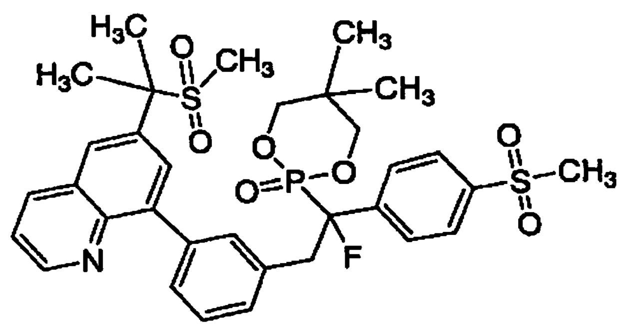


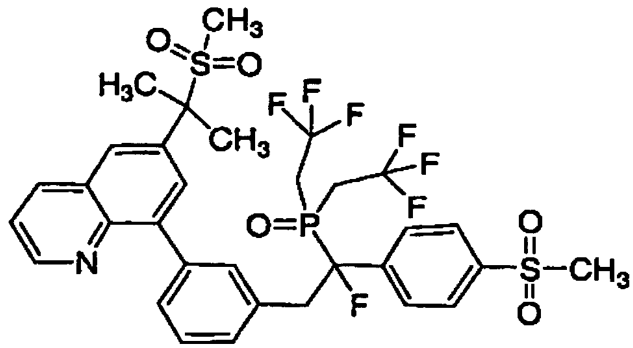








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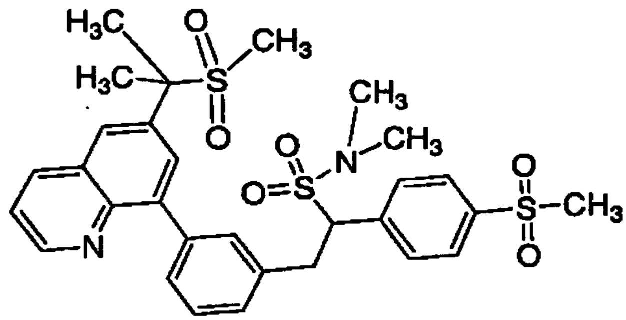
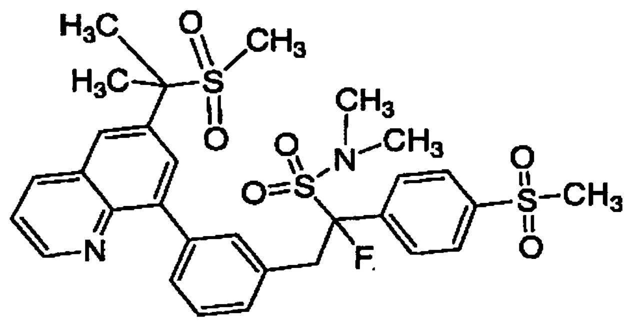
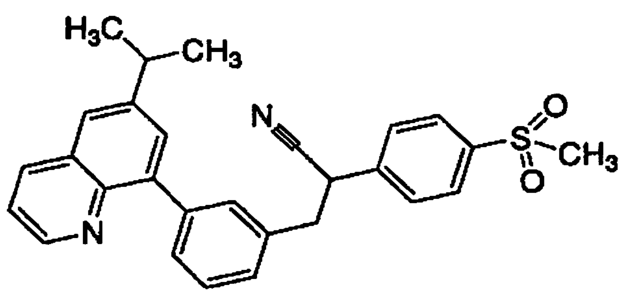
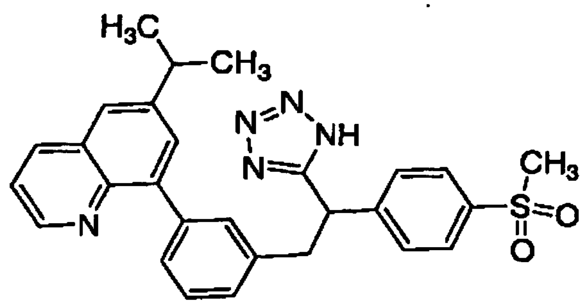
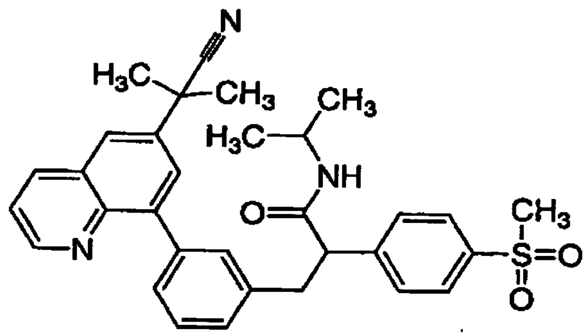
O=S=O
H3C
CH3
F F F
F F F
O=P
N
F
S-CH3
O O

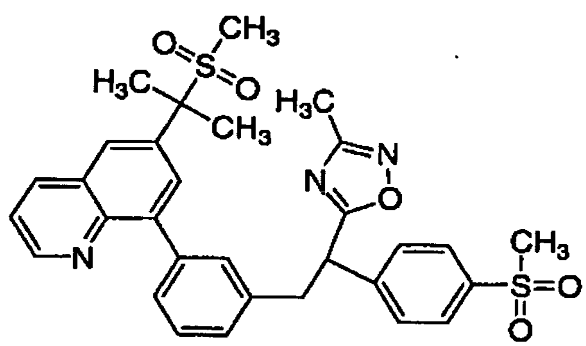

H3C
H3C
O
S
O
CH3
CH3
N
CH3
O=S
O
N
S-CH3
O O

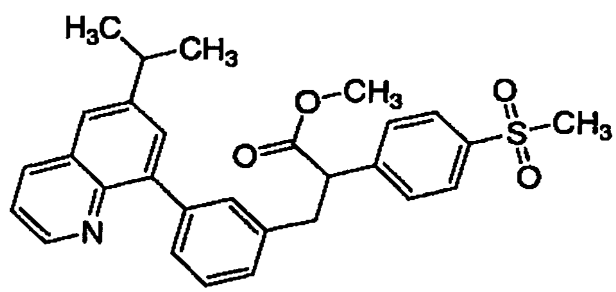

H3C
H3C
O
S
O
CH3
CH3
N
CH3
O=S
O
N
F
S-CH3
O O

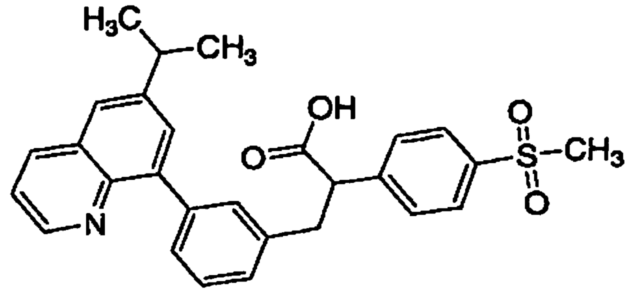

H3C
CH3
N
N
S
O O
CH3










H3C
CH3
OH
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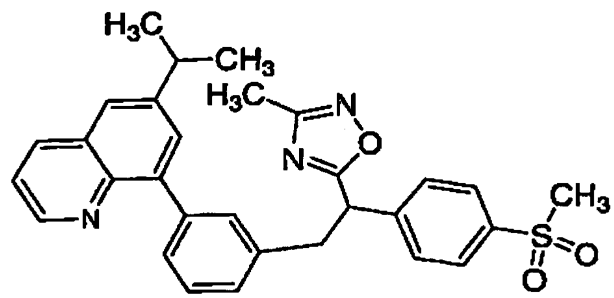
O
S
CH3
O
N


H3C
CH3
H3C
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O
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CH3
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O
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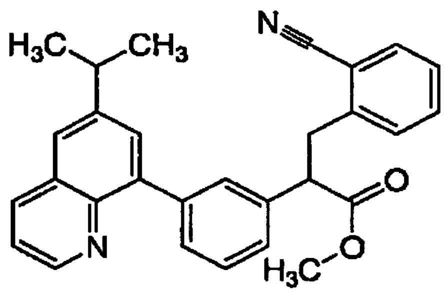
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H3C
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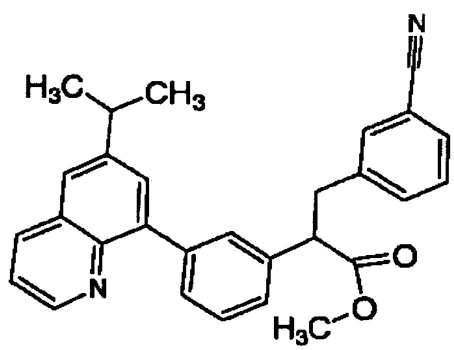
N
H3C
CH3
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H3C
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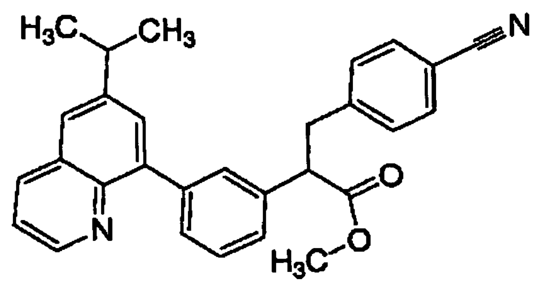
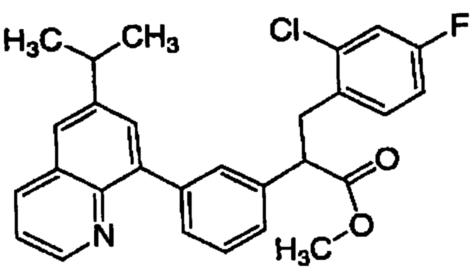
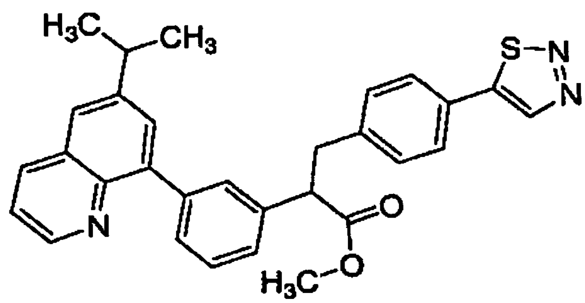
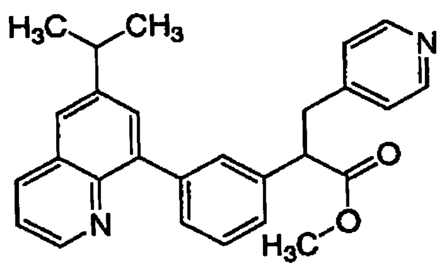
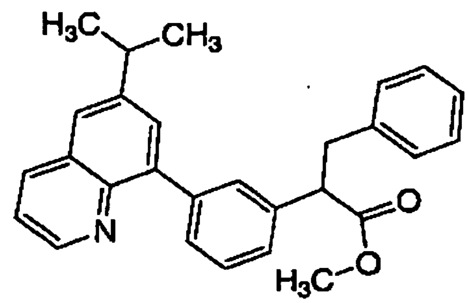
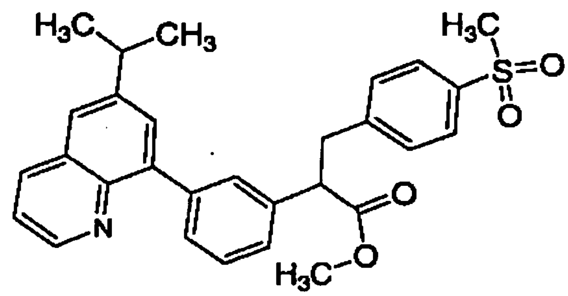


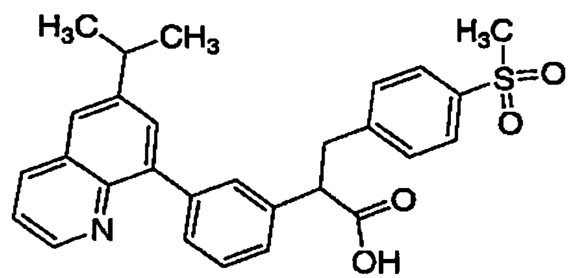


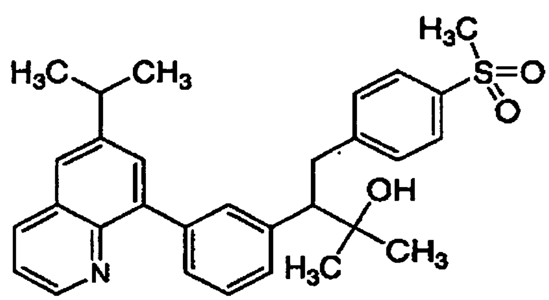


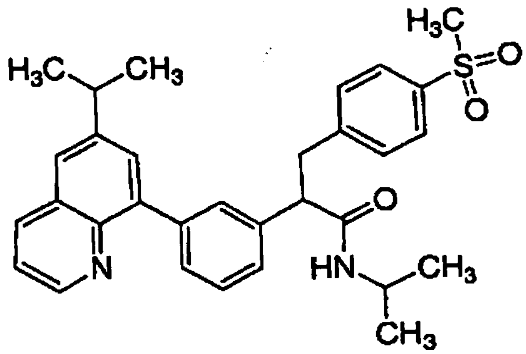


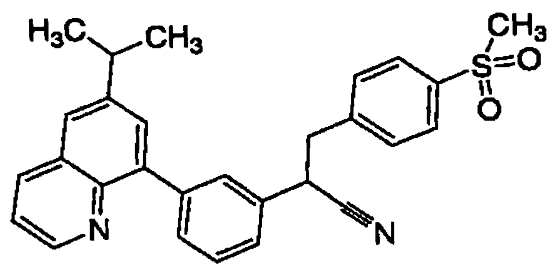


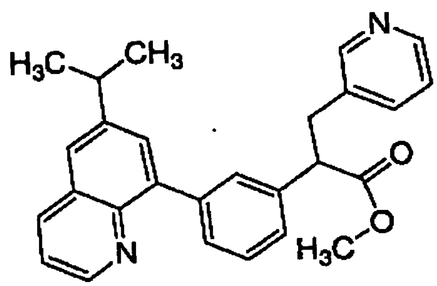







H3C
CH3
H3C
S
O
O
O
N
HN
CH3
CH3


H3C
CH3
CH3
S
O
O
N
N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CH3
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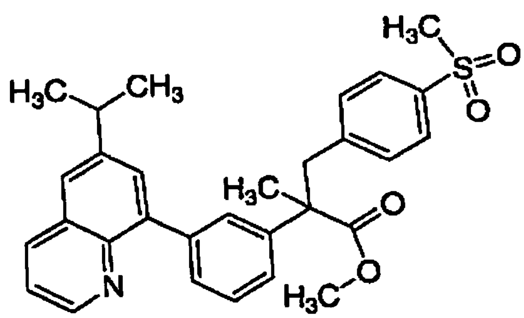
O
N
H3C


H3C
CH3
H3C
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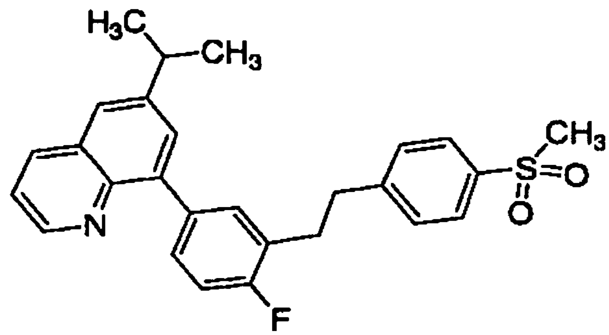
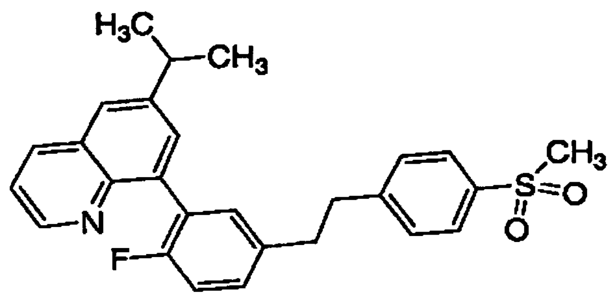
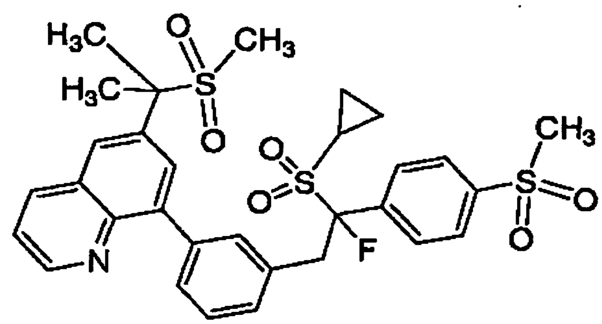
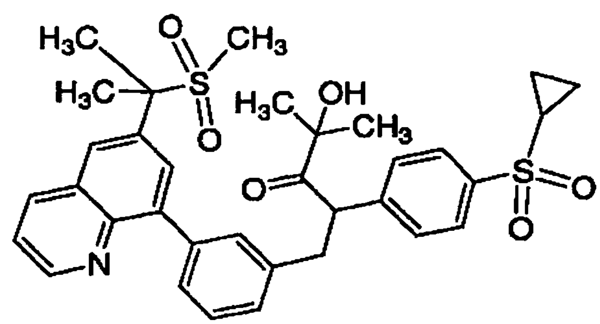
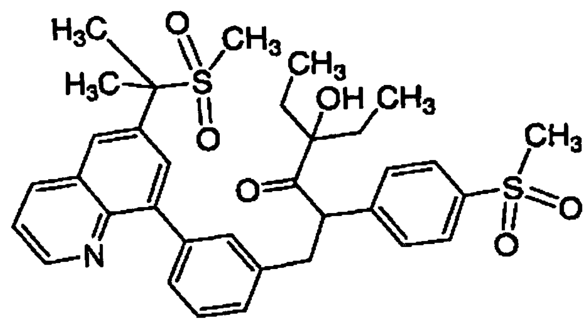
O
N
H3C





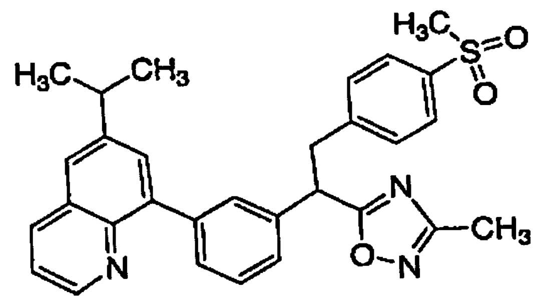






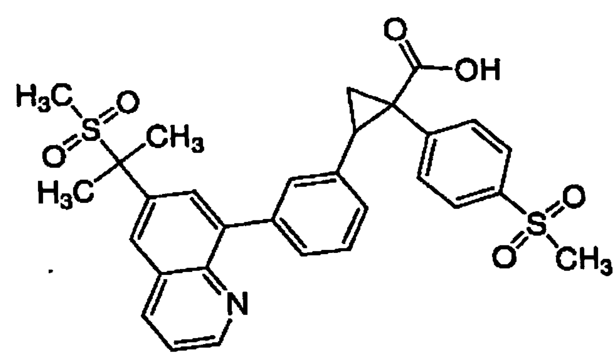
or a pharmaceutically acceptable salt thereof.

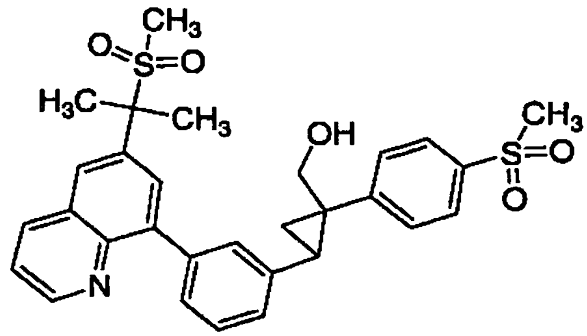
11. The compound according to Claim 1 represented by

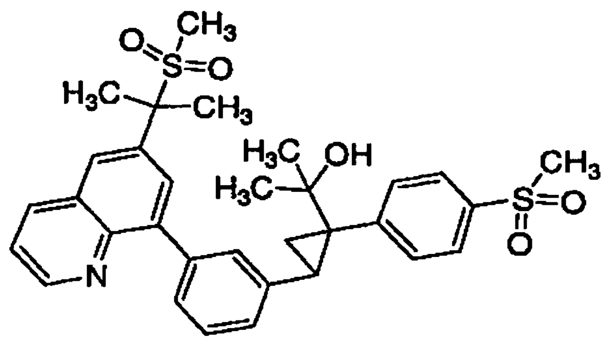


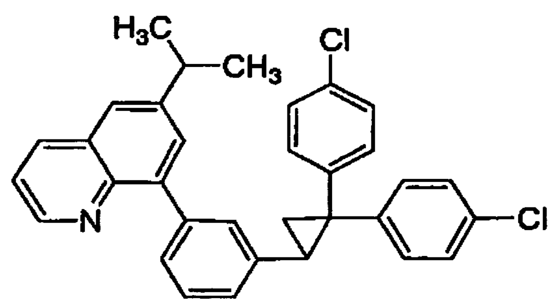
or a pharmaceutically acceptable salt thereof.

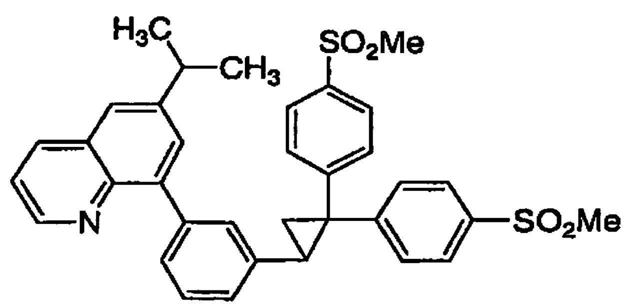
12. The compound according to Claim 1 represented by





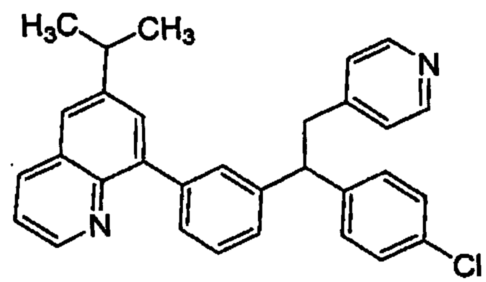


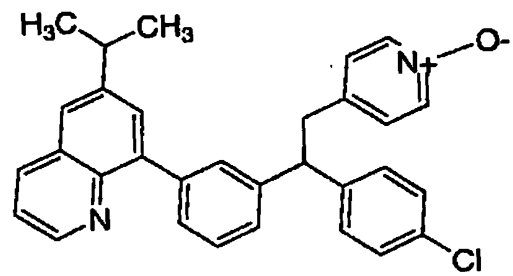


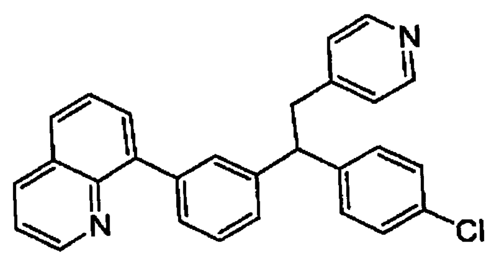


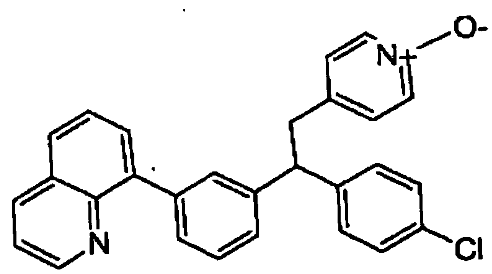
or a pharmaceutically acceptable salt thereof.

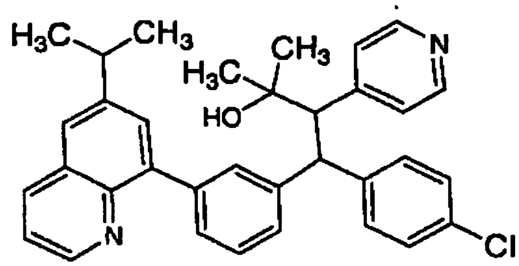
13. The compound according to Claim 1 represented by

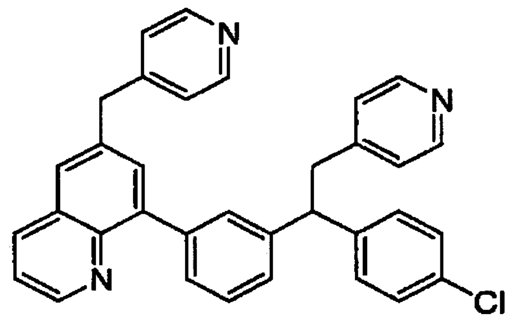






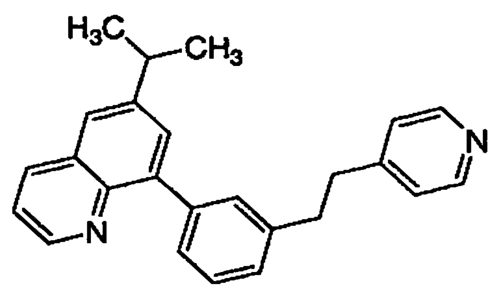


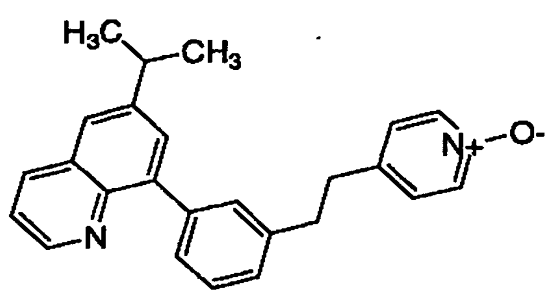


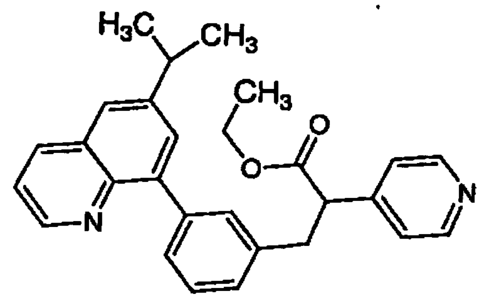


or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 1 represented by



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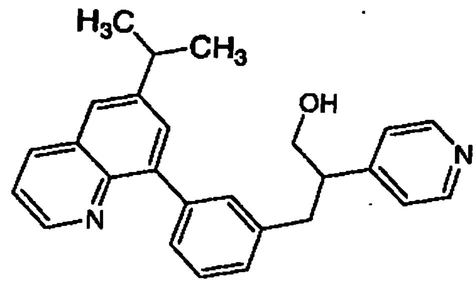
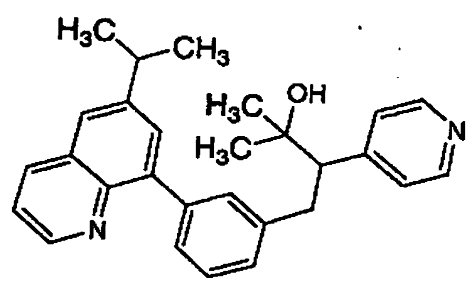
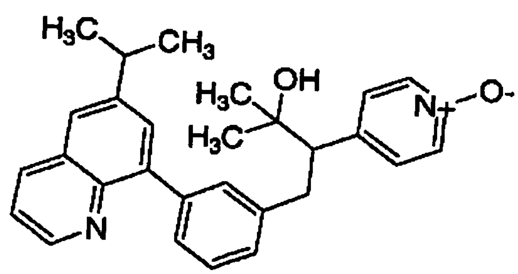
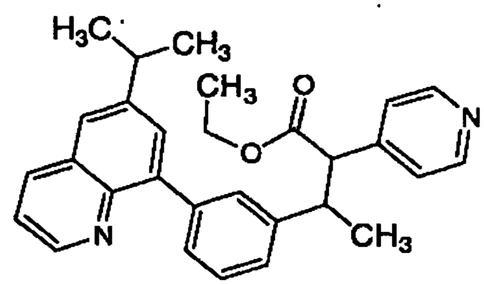
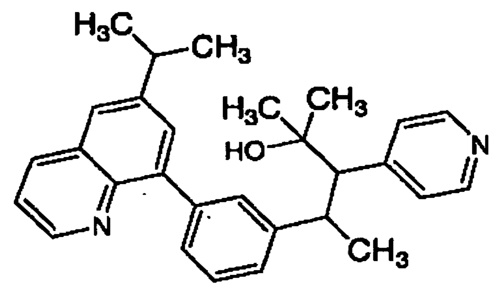
CH3
CH3
O
O
N
N

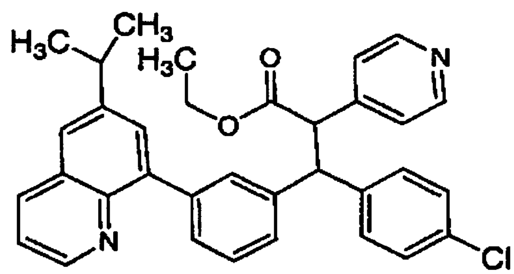

H3C
CH3
OH
N
N

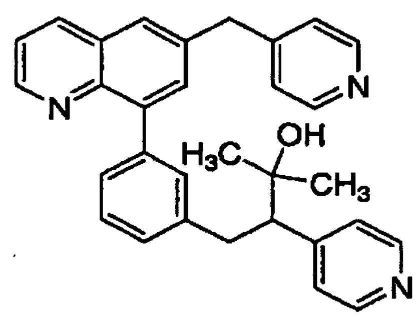

H3C
CH3
H3C
OH
H3C
N
N

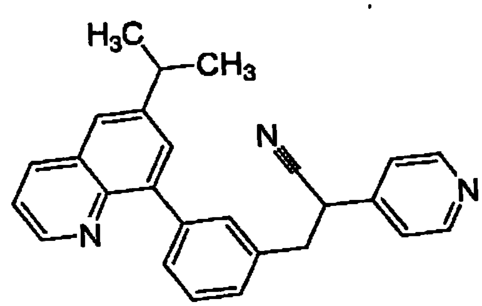

H3C
CH3
H3C
OH
H3C
N+
O-
N





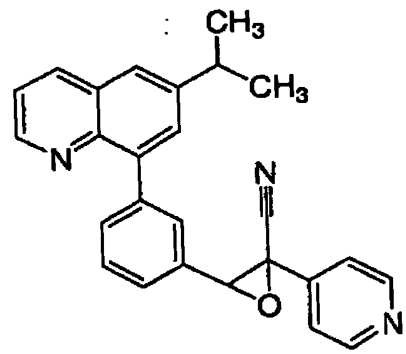


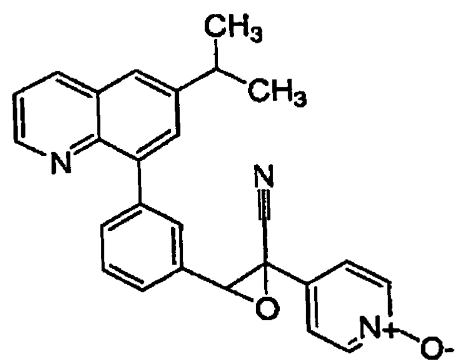


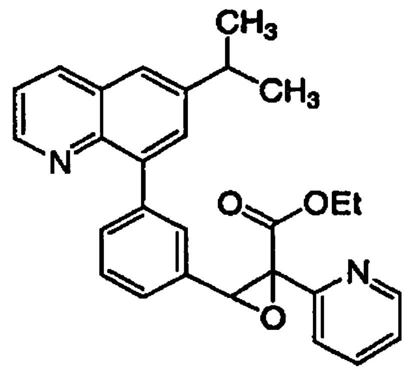


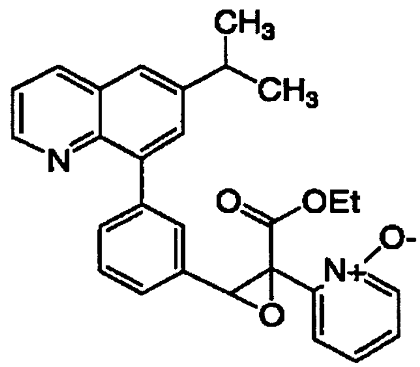
or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 1 represented by









or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of

the compound according to any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier.

17. The pharmaceutical composition according to claim 16, further comprising a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, an M2/M3 antagonist, a corticosteroid, an H1 receptor antagonist or a beta 2 adrenoceptor agonist.

18. The pharmaceutical composition according to claim 16, further comprising a COX-2 selective inhibitor, a statin, or an NSAID.

19. A method of treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

20. A method of treatment or prevention of eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic dermatitis comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

21. A method of treatment or prevention of laminitis in horses, or colic in horses comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

22. A method of treatment or prevention of endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

23. A method of treatment or prevention of Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

24. A method of treatment or prevention of adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

25. A method of treatment or prevention of monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

26. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof for use in treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic dermatitis, laminitis in horses, or colic in horses, endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis.

27. Use of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament of treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic dermatitis, laminitis in horses, or colic in horses, endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue

degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis.

28. A pharmaceutical composition for treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic dermatitis, laminitis in horses, or colic in horses, endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis comprising a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 02/00953

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47 C07D215/12 C07D401/10 C07D405/10 C07D417/12
C07F9/60 C07F9/6571 C07D403/10 C07D413/10 C07D417/10
C07D405/14 A61P11/06 A61P29/00 A61P17/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 46151 A (MASTRACCHIO ANTHONY ;MERCK FROSST CANADA INC (CA); DUBE DANIEL (CA) 28 June 2001 (2001-06-28) claim 1	1-28
A	US 5 455 252 A (WILHELM ROBERT S ET AL) 3 October 1995 (1995-10-03) claim 1	1-28

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 2002	17/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

.....rnational application No.
PCT/CA 02/00953

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 02/00953

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0146151	A	28-06-2001	AU	2336201	A	03-07-2001
			WO	0146151	A1	28-06-2001
			US	6410563	B1	25-06-2002
			US	2002103226	A1	01-08-2002
US 5455252	A	03-10-1995	AT	170855	T	15-09-1998
			AU	679222	B2	26-06-1997
			AU	6412994	A	24-10-1994
			CA	2159603	A1	13-10-1994
			DE	69413215	D1	15-10-1998
			DE	69413215	T2	28-01-1999
			DK	691966	T3	08-02-1999
			EP	0691966	A1	17-01-1996
			ES	2120028	T3	16-10-1998
			FI	954651	A	29-09-1995
			HU	9500111	A3	28-06-1995
			HU	73181	A2	28-06-1996
			JP	8511238	T	26-11-1996
			NO	953879	A	22-11-1995
			NZ	263436	A	22-08-1997
			WO	9422852	A1	13-10-1994